Special article

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European Code Against Cancer and scientific justification: third version (2003)

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Introduction

Since the previous version of the *European Code Against Cancer* was created [1], the European Union has expanded its number of Member States and next year (in 2004) will see a further and dramatic expansion as 10 new Member States join (Cyprus, Czech Republic, Hungary, Estonia, Malta, Latvia, Lithuania, Poland, Slovenia and Slovakia). Additionally, it is currently anticipated that Bulgaria and Romania will be admitted in 2007 followed at a later date by Turkey. These expansions enlarge the Union to incorporate a greater diversity of peoples with a much larger degree of heterogeneity present in lifestyle habits and disease risk than previously present. The contrast between the Mediterranean countries, the Nordic countries and those countries of Central and Eastern Europe is considerable. In view of the accession of new States, an important aspect of the revision of this Code was to take into consideration the specific situation in new Member States.

For the purposes of this text, the European Union shall be defined as the 15 current Member States (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, The Netherlands, Portugal, Spain, Sweden and the UK) plus the 10 Accession Countries scheduled for entry in 2004 (Cyprus, Czech Republic, Hungary, Estonia, Malta, Latvia, Lithuania, Poland, Slovenia and Slovakia).

European Union cancer burden

In the European Union in 2000, it is estimated that there were 1 892 000 incident cases of all forms of cancer (excluding non-melanoma skin cancers) diagnosed (Table 1): this burden was shared almost equally by each gender, although there was a slight excess in men (1 014 000 cases) over women (878 000 cases). In 2000, it is estimated that there were 1 156 000 deaths in the

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European Union where cancer was the underlying cause. Of these, 651 000 were of men and 504 000 women (Table 1).

The commonest form of cancer diagnosed in the European Union in 2000 was colorectal cancer, with an estimated total of 258 000 new cases. Of these, 123 000 were diagnosed in men while 135 000 were in women (Table 2). There was a total of 138 000 deaths caused by colorectal cancer in the European Union, of which 70 000 were of men and 68 000 women (Table 2).

In 2000, it is estimated that there were 241 000 incident cases of lung cancer, with the majority diagnosed in men (192 000 cases) and fewer in women (49 000 cases) (Table 3). In the same year, it is estimated that there were 231 000 deaths in the European Union caused by lung cancer. Of these, 183 000 occurred in men and 49 000 in women.

There was an estimated 95 500 incident cases of stomach cancer diagnosed in 2000, of which 57 000 were diagnosed in men and 38 000 in women (Table 4). There was an estimated total of 78 000 deaths caused by stomach cancer: 45 000 in men and 32 500 in women (Table 4).

In women, there was an estimated 244 500 new cases of breast cancer diagnosed in the year 2000 and there were 91 000 deaths caused by breast cancer (Table 5). In men, there was an estimated total of 157 000 incident cases of prostate cancer diagnosed in the European Union in 2000 and an estimated 66 500 deaths caused by this disease (Table 5).

The age-adjusted risk of cancer increases quite quickly with age [2]: there is a difference of at least two orders of magnitude between the risk of developing cancer in the fourth decade of life and the eighth decade of life. Even if age-specific cancer rates remain fixed at 1980 levels, it is to be expected that there will be large increases in the numbers of cases of cancer diagnosed for the first two decades of the twenty-first century. This is simply a consequence of the ageing population; more and more men and women living to older and older ages. The postworld war II 'baby-boom', the first generation in Western Europe to have had the benefit of modern medicine and not to have endured a major war, will reach ages where cancer is an important problem from the early days of this century. The effect on the absolute numbers of cases will be quite dramatic, particularly for cancer sites, such as prostate cancer, where the median age at diagnosis is currently ~75 years, in the European Union [3].

Cancer control

The diseases grouped under the title 'cancer' are remarkably common and of major public health importance since more than half the people who develop cancer die from their disease. Thus, the concept of 'cancer control' has been developed to attack the cancer problem at various points in its evolution, with the overall goal of reducing cancer related suffering and death.

Primary prevention. The most obvious ways to prevent people dying from cancer are either to find cures for the different forms of the disease, or to find ways to stop the development of clinical cancer in the first instance. At the present time, cancer prevention involves determining the causes of cancer (risk determinants) from among those factors shown to be associated with the

Table 1. Estimates of numbers of incidence cases and cancer deaths from all forms of cancer combined in men and women in Europe, 2000

	Country	Men		Women	
		Cases	Deaths	Cases	Deaths
EU	Austria	16 161	10 105	15 495	9470
	Belgium	26 468	16 697	21 480	12 151
	Denmark	11 364	8013	13 277	7531
	Finland	9841	5700	9986	4958
	France	149 004	92 541	108 132	59 296
	Germany	201 944	118 899	184 649	107 213
	Greece	21 045	14 782	15 354	9171
	Ireland	6388	4086	6102	3621
	Italy	141 738	91 397	119 029	65 021
	Luxembourg	962	605	853	471
	The Netherlands	34 119	21 425	31 852	17 296
	Portugal	19 611	11 902	16 488	8706
	Spain	84 736	57 800	58 699	34 963
	Sweden	20 653	11 626	20 227	10 250
	UK	123 791	84 722	123 876	76 923
	EU	**867 825**	**550 300**	**745 499**	**427 041**
EEA	Iceland	496	252	471	257
	Norway	9870	5672	9285	4886
	Switzerland	15 675	9822	13 258	7479
	EEA	**26 041**	**15 746**	**23 014**	**12 622**
EU + EEA	**EU + EEA**	**893 866**	**566 046**	**768 513**	**439 663**
APP	Cyprus	1135	775	862	488
	Czech Republic	23 582	15 856	21 572	12 465
	Estonia	2482	1741	2422	1432
	Hungary	27 683	18 948	24 780	14 704
	Latvia	3452	2796	3889	2482
	Lithuania	5645	4300	5384	3265
	Malta	626	426	617	328
	Poland	68 165	47 101	61 391	35 163
	Slovakia	9835	6775	8141	4670
	Slovenia	3910	2774	3683	2232
	Accession states	**146 515**	**101 492**	**132 741**	**77 229**
WAI	Bulgaria	14 122	9490	12 213	6793
	Romania	32 817	22 383	29 984	15 977
	Turkey	40 976	30 560	26 240	15 566
	Waiting list	**87 915**	**62 433**	**68 437**	**38 336**
Other	Albania	3575	2192	2911	1371
	Bosnia Herzegovina	6078	3745	5377	2607
	Croatia	10 201	7499	8383	4720
	Macedonia	2449	1683	2039	1143
	Yugoslavia	17 903	10 146	15 742	7551
	Balkans	**40 206**	**25 265**	**34 452**	**17 392**
Eastern	Belarus	16 854	11 603	13 256	7813
	Moldova	5250	3465	5181	2639
	Russian Federation	240 809	170 132	229 475	131 573
	Ukraine	83 332	57 797	77 655	42 816
	Eastern countries	**346 245**	**242 997**	**325 567**	**184 841**

All but skin cancer estimates for 2000.
EU, European Union; EEA, European Economic Area; APP, accession states; WAI, waiting list.
Source: Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2000: Cancer incidence, mortality and prevalence worldwide, Version 1.0. IARC CancerBases No. 5. Lyon, France: International Agency for Research on Cancer 2001.

Table 2. Estimates of numbers of incidence cases and cancer deaths of colorectal cancer in men and women in Europe, 2000

	Country	Men		Women	
		Cases	Deaths	Cases	Deaths
EU	Austria	2568	1407	2197	1353
	Belgium	3121	1589	3073	1719
	Denmark	1674	1056	1647	1067
	Finland	969	491	1091	549
	France	18313	8915	16202	8221
	Germany	30359	14929	30454	17342
	Greece	1728	880	1570	839
	Ireland	1049	546	807	459
	Italy	17841	8739	15474	8034
	Luxembourg	122	64	129	70
	The Netherlands	4836	2254	4463	2210
	Portugal	3072	1461	2423	1211
	Spain	10502	5951	8664	5001
	Sweden	2731	1234	2468	1219
	UK	17249	9341	15924	9047
	EU	**116134**	**58857**	**106586**	**58341**
EEA	Iceland	54	23	43	28
	Norway	1427	812	1502	841
	Switzerland	1787	1042	1713	907
	EEA	**3268**	**1877**	**3258**	**1776**
EU + EEA	**EU + EEA**	**119402**	**60734**	**109844**	**60117**
APP	Cyprus	89	44	83	43
	Czech Republic	4325	2477	3130	1955
	Estonia	250	147	299	185
	Hungary	4235	2420	3642	2314
	Latvia	371	260	498	364
	Lithuania	557	404	603	404
	Malta	73	46	73	40
	Poland	6916	3883	6411	3994
	Slovakia	1578	885	1156	726
	Slovenia	539	347	490	308
	Accession states	**18933**	**10913**	**16385**	**10333**
WAI	Bulgaria	2116	1202	1633	996
	Romania	3220	1792	2669	1614
	Turkey	2472	1599	1528	984
	Waiting list	**7808**	**4593**	**5830**	**3594**
Other	Albania	436	238	314	169
	Bosnia Herzegovina	756	410	609	329
	Croatia	1353	831	1038	615
	Macedonia	216	137	172	110
	Yugoslavia	2231	1158	1850	987
	Balkans	**4992**	**2774**	**3983**	**2210**
Eastern	Belarus	1708	1008	1855	1080
	Moldova	656	350	576	334
	Russian Federation	25749	14162	29587	18012
	Ukraine	9821	5392	9491	5704
	Eastern countries	**37934**	**20912**	**41509**	**25130**

EU, European Union; EEA, European Economic Area; APP, accession states; WAI, waiting list.
Source: Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2000: Cancer incidence, mortality and prevalence worldwide, Version 1.0. IARC CancerBases No. 5. Lyon, France: International Agency for Research on Cancer 2001.

Table 3. Estimates of numbers of incidence cases and cancer deaths of lung cancer in men and women in Europe, 2000

	Country	Men		Women	
		Cases	Deaths	Cases	Deaths
EU	Austria	2451	2487	889	866
	Belgium	6256	5958	1055	968
	Denmark	1999	2182	1336	1349
	Finland	1443	1630	450	400
	France	22910	21652	3833	3802
	Germany	33568	31294	9403	8478
	Greece	5269	4855	898	834
	Ireland	941	922	538	515
	Italy	29937	27273	5689	5484
	Luxembourg	191	183	47	43
	The Netherlands	7249	7092	2207	1968
	Portugal	2474	2190	512	472
	Spain	16821	15974	1552	1694
	Sweden	1737	1896	1058	1176
	UK	23708	24433	13423	13231
	EU	**156954**	**150021**	**42890**	**41280**
EEA	Iceland	58	54	47	45
	Norway	1231	1135	649	524
	Switzerland	2698	2334	745	654
	EEA	**3987**	**3523**	**1441**	**1223**
EU + EEA	**EU + EEA**	**160941**	**153544**	**44331**	**42503**
APP	Cyprus	283	257	49	44
	Czech Republic	4905	4651	1181	1088
	Estonia	606	560	138	126
	Hungary	6526	5943	2100	1887
	Latvia	880	849	161	167
	Lithuania	1273	1247	213	208
	Malta	117	120	17	15
	Poland	17771	16303	3948	3557
	Slovakia	2100	1873	379	332
	Slovenia	875	758	202	197
	Accession states	**35336**	**32561**	**8388**	**7621**
WAI	Bulgaria	2968	2692	619	560
	Romania	7352	6608	1510	1350
	Turkey	10418	95968	1152	1056
	Waiting list	**20738**	**105268**	**3281**	**2966**
Other	Albania	1035	710	183	126
	Bosnia Herzegovina	1842	1238	366	247
	Croatia	2682	2283	532	430
	Macedonia	563	473	111	89
	Yugoslavia	5842	3495	1156	732
	Balkans	**11964**	**8199**	**2348**	**1624**
Eastern	Belarus	4214	3526	487	429
	Moldova	1027	918	214	191
	Russian Federation	60455	55040	10477	9507
	Ukraine	19336	17537	3504	3162
	Eastern countries	**85032**	**77021**	**14682**	**13289**

EU, European Union; EEA, European Economic Area; APP, accession states; WAI, waiting list.
Source: Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2000: Cancer incidence, mortality and prevalence worldwide, Version 1.0. IARC CancerBases No. 5. Lyon, France: International Agency for Research on Cancer 2001.

Table 4. Estimates of numbers of incidence cases and cancer deaths of stomach cancer in men and women in Europe, 2000

	Country	Men		Women	
		Cases	Deaths	Cases	Deaths
EU	Austria	947	867	778	774
	Belgium	982	777	664	588
	Denmark	352	323	219	196
	Finland	445	402	355	324
	France	5109	3825	2878	2498
	Germany	10900	8805	8627	7767
	Greece	1113	848	733	568
	Ireland	304	242	178	146
	Italy	10206	7742	7026	5525
	Luxembourg	40	32	29	26
	The Netherlands	1498	1113	782	708
	Portugal	2235	1700	1485	1150
	Spain	5708	4213	3602	2869
	Sweden	731	622	461	431
	UK	6178	5101	3579	3199
	EU	**46748**	**36612**	**31396**	**26769**
EEA	Iceland	24	19	11	12
	Norway	423	362	259	265
	Switzerland	703	508	382	343
	EEA	**1150**	**889**	**652**	**620**
EU + EEA	**EU + EEA**	**47898**	**37501**	**32048**	**27389**
APP	Cyprus	58	44	38	29
	Czech Republic	1145	978	896	780
	Estonia	250	211	202	158
	Hungary	1794	1510	1319	1110
	Latvia	394	349	335	273
	Lithuania	619	540	450	346
	Malta	35	35	19	15
	Poland	5338	4471	2964	2491
	Slovakia	642	535	397	322
	Slovenia	312	277	186	196
	Accession states	**10587**	**8950**	**6806**	**5720**
WAI	Bulgaria	1404	1180	921	777
	Romania	3267	2731	1654	1396
	Turkey	2785	2382	1655	1412
	Waiting list	**7456**	**6293**	**4230**	**3585**
Other	Albania	264	188	138	102
	Bosnia Herzegovina	456	317	271	195
	Croatia	902	718	538	431
	Macedonia	370	267	192	134
	Yugoslavia	1261	794	761	513
	Balkans	**3253**	**2284**	**1900**	**1375**
Eastern	Belarus	2913	2046	1935	1416
	Moldova	546	449	328	276
	Russian Federation	34714	28785	25298	21313
	Ukraine	10441	8657	6510	5493
	Eastern countries	**48614**	**39937**	**34071**	**28498**

EU, European Union; EEA, European Economic Area; APP, accession states; WAI, waiting list.
Source: Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2000: Cancer incidence, mortality and prevalence worldwide, Version 1.0. IARC CancerBases No. 5. Lyon, France: International Agency for Research on Cancer 2001.

Table 5. Estimates of numbers of incidence cases and cancer deaths of prostate cancer in men and breast cancer in women in Europe, 2000

	Country	Prostate (men)		Breast (women)	
		Cases	Deaths	Cases	Deaths
EU	Austria	3102	1216	4359	1754
	Belgium	5128	1881	6813	2512
	Denmark	1422	1069	3648	1412
	Finland	2923	785	3272	834
	France	28342	10104	37193	11529
	Germany	37904	13348	51710	19149
	Greece	2273	1240	4254	1660
	Ireland	1177	547	1711	666
	Italy	14197	7105	32037	11902
	Luxembourg	168	58	237	89
	The Netherlands	6745	2486	10880	3711
	Portugal	3086	1541	4324	1596
	Spain	8954	5803	14934	6381
	Sweden	6156	2508	6012	1528
	UK	21302	10062	34815	14415
	EU	**142879**	**59753**	**216199**	**79138**
EEA	Iceland	142	32	123	70
	Norway	2449	1063	2334	812
	Switzerland	3437	1672	4071	1682
	EEA	**6028**	**2767**	**6528**	**2564**
EU + EEA	**EU + EEA**	**148907**	**62520**	**222727**	**81702**
APP	Cyprus	111	60	247	93
	Czech Republic	2695	1186	4598	1976
	Estonia	343	138	516	228
	Hungary	2925	1370	5579	2384
	Latvia	316	191	839	385
	Lithuania	709	363	1123	582
	Malta	73	37	200	91
	Poland	5920	2708	12648	4980
	Slovakia	922	465	1737	761
	Slovenia	465	267	929	360
	Accession states	**14479**	**6785**	**28416**	**11840**
WAI	Bulgaria	1450	665	2961	1194
	Romania	3076	1417	7107	2767
	Turkey	1737	1050	6123	2751
	Waiting list	**6263**	**3132**	**16191**	**6712**
Other	Albania	204	129	757	258
	Bosnia Herzegovina	335	221	1373	490
	Croatia	740	535	2024	825
	Macedonia	160	88	500	219
	Yugoslavia	958	593	3890	1399
	Balkans	**2397**	**1566**	**8544**	**3191**
Eastern	Belarus	1096	518	2945	1160
	Moldova	273	113	1490	523
	Russian Federation	12869	5553	52185	19843
	Ukraine	5159	2195	19722	7472
	Eastern countries	**19397**	**8379**	**76342**	**28998**

EU, European Union; EEA, European Economic Area; APP, accession states; WAI, waiting list.
Source: Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2000: Cancer incidence, mortality and prevalence worldwide, Version 1.0. IARC CancerBases No. 5. Lyon, France: International Agency for Research on Cancer 2001.

development of the disease by epidemiological studies (risk factors). Avoiding exposure to risk determinants would result in a reduction in cancer risk.

The evidence that cancer is preventable is compelling. Different populations around the world experience different levels of different forms of cancer [4], and these levels change with time in orderly and predictable manners [5]. Groups of migrants quickly leave behind the cancer levels of their original home and acquire the cancer pattern of their new residence, sometimes within one generation [6, 7]. Thus, those Japanese who left Japan for California left behind the high levels of gastric cancer in their homeland and exchanged it for the high levels of breast and colorectal cancer present among inhabitants of their new home. Furthermore, groups whose lifestyle habits differentiate themselves from other members of the same community frequently have different cancer risks (c.f. Seventh Day Adventist and Mormons [8]).

For reasons such as these, it is estimated that upwards of 80%, or even 90%, of cancers in western populations may be attributable to environmental causes [9]; defining 'environment' in its broadest sense to include a wide range of ill-defined dietary, social and cultural practices. Although all of these avoidable causes have not yet been clearly identified, it is thought that risk determinants currently exist for about one half of cancers. Thus, primary prevention in the context of cancer is an important area of public health.

Secondary prevention. It is very frequently the case that the probability of successful treatment of cancer is increased, sometimes very substantially, if the cancer can be diagnosed at an early stage. Awareness of the significance of signs and symptoms is important, but all too frequently cancers that exhibit symptoms are at an advanced stage. 'Screening' is a term frequently applied to the situation where tests are used to indicate whether an (generally asymptomatic) individual has a high or low chance of having a cancer. Detecting cancers at an early, asymptomatic stage could lead to decreases in the mortality rates for certain cancers, particularly for those forms of cancer in which early detection prevents metastatic dissemination.

Tertiary prevention. An obvious way to prevent cancer death is to cure those cancers which develop. However, there have been few major breakthroughs in cancer treatment, in the sense of turning a fatal tumour into a curable one. Notable successes have been in testicular teratoma [10], Hodgkin's disease (HD) [11], childhood leukaemia, Wilm's tumour and choriocarcinoma. Progress in survival from the major cancers has been very much less than hoped. Adjuvant chemotherapy and tamoxifen have improved survival in breast cancer [12], adjuvant chemotherapy has also contributed to improvements in the prognosis of ovarian cancer and colorectal cancer [13], and there has been some other progress that could be attributed specifically to certain treatments.

General progress in medical science has led to modern anaesthesia making more patients candidates for surgery and surgery safer, better control of infection and bacterial diseases, better imaging has improved tumour localisation and staging, and better devices are available to deliver the appropriate doses of radiation and drugs. Thus, more patients can receive better and more appropriate therapy and, hence, have a better prognosis.

The quality-of-life issue has not been neglected, with breast conservation therapy now almost supplanting traditional radical mastectomy in the majority of women; more plastic breast reconstruction; less amputation of limbs for bone and soft-tissue sarcomas; and better colostomies, being some important advances.

Against this background of cancer as an important public health problem and one of the commonest causes of premature and avoidable death in Europe, the *European Code Against Cancer* was introduced as a series of recommendations which, if followed, could lead in many instances to a reduction in cancer incidence and also to reductions in cancer mortality.

The *European Code Against Cancer* was originally drawn-up, and subsequently endorsed by the European Commission high-level Committee of Cancer Experts, in 1987. In 1994, the European Commission invited the European School of Oncology to assemble a group of international experts to examine, and consider revision of, the scientific aspects of the recommendations given in the current code. This exercise took place and a new version was adopted by the Cancer Experts Committee at its meeting in November 1994 [1].

This publication constitutes the second revision, producing the third version, of the *European Code Against Cancer*. The project was funded by the *Europe Against Cancer* programme of the European Commission. An Executive Committee was formed to guide the project and the committee involved public health specialists, oncologists, as well as representatives of the Cancer Leagues and the Prevention Departments of Ministries of Health in Europe. A Scientific Committee was established comprising several independent experts and nominated chairmen of the subcommittees established to review recommendations on specific topics. More than 100 medical scientists contributed to the development of this revision. Below the scientific rationale for each recommended point of the *European Code Against Cancer* is outlined, as well as discussion of other factors that were considered but not included in the code.

Many aspects of general health can be improved, and many cancer deaths prevented, if we adopt healthier lifestyles

Any recommendation made to reduce cancer occurrence should not be one which could lead to an increased risk of other diseases. The recommendations which comprise the revised *European Code Against Cancer* should, if followed, also lead to improvements in other aspects of general health (Table 6). It is also important to recognise from the outset that each individual has choices to make about their lifestyle, some of which could lead to a reduction in their risk of developing cancer. These choices, and the rationale underlying their recommendation, are presented below.

1. Do not smoke; if you smoke, stop doing so. If you fail to stop, do not smoke in the presence of non-smokers.

It is estimated that between 25 and 30% of all cancer deaths in developed countries are tobacco-related. From the results of stud-

Table 6. European Code Against Cancer (third version)

	Many aspects of general health can be improved, and many cancer deaths prevented, if we adopt healthier lifestyles:
1.	Do not smoke; if you smoke, stop doing so. If you fail to stop, do not smoke in the presence of non-smokers.
2.	Avoid obesity.
3.	Undertake some brisk, physical activity every day.
4.	Increase your daily intake and variety of vegetables and fruits: eat at least five servings daily. Limit your intake of foods containing fats from animal sources.
5.	If you drink alcohol, whether beer, wine or spirits, moderate your consumption to two drinks per day if you are a man or one drink per day if you are a woman.
6.	Care must be taken to avoid excessive sun exposure. It is specifically important to protect children and adolescents. For individuals who have a tendency to burn in the sun active protective measures must be taken throughout life.
7.	Apply strictly regulations aimed at preventing any exposure to known cancer-causing substances. Follow all health and safety instructions on substances which may cause cancer. Follow advice of National Radiation Protection Offices.
	There are public health programmes that could prevent cancers developing or increase the probability that a cancer may be cured:
8.	Women from 25 years of age should participate in cervical screening. This should be within programmes with quality control procedures in compliance with *European Guidelines for Quality Assurance in Cervical Screening*.
9.	Women from 50 years of age should participate in breast screening. This should be within programmes with quality control procedures in compliance with *European Guidelines for Quality Assurance in Mammography Screening*.
10.	Men and women from 50 years of age should participate in colorectal screening. This should be within programmes with built-in quality assurance procedures.
11.	Participate in vaccination programmes against hepatitis B virus infection.

Table 7. Hazards for the individual cigarette user

Big risk, especially among those who start smoking cigarettes regularly in their **teenage** years: if they keep smoking steadily then about **half** will eventually be killed by tobacco (approximately one-quarter in old age plus one-quarter in middle age)
Those killed by tobacco in **middle** age (35–69 years) lose an average of **20–25 years** of non-smoker life expectancy
Throughout the European Union, tobacco is much the greatest single cause of death. In non-smokers, cancer mortality is decreasing slowly and total mortality is decreasing rapidly
Most of those killed by tobacco were not particularly 'heavy' smokers
Stopping smoking works: Even in middle age, stopping *before* having cancer or some other serious disease avoids *most* of the later excess risk from tobacco, and the benefits of stopping at earlier ages are even greater

This table has been adapted from the following source: Peto R, Lopez AD, Boreham J, Thun M, Heath C. Mortality from Smoking in Developed Countries 1950–2000. Oxford, UK: Oxford Medical Publications 1994.

ies conducted in Europe, Japan and North America, between 87 and 91% of lung cancers in men, and between 57 and 86% of lung cancers in women, are attributable to cigarette smoking. For both sexes combined, the proportion of cancers arising in the oesophagus, larynx and oral cavity attributable to the effect of tobacco, either acting singly or jointly with the consumption of alcohol, is between 43 and 60%. A large proportion of cancers of the bladder and pancreas and a small proportion of cancers of the kidney, stomach, cervix and nose, and myeloid leukaemia are also causally related to tobacco consumption. Because of the length of the latency period, tobacco-related cancers observed today are related to the cigarette smoking patterns over several previous decades. On stopping smoking, the increase in risk of cancer induced by smoking rapidly ceases. Benefit is evident within 5 years and is progressively more marked with the passage of time.

Smoking also causes many other diseases, most notably chronic obstruction pulmonary disease (commonly called chronic bronchitis) and an increased risk of both heart disease and stroke. The death rate of long-term cigarette smokers in middle age (35–69 years of age) is three times that of life-long non-smokers; and approximately half of regular cigarette smokers, who started smoking early in life, eventually die because of their habit. Half the deaths take place in middle age, when the smokers lose ~20–25 years of life expectancy compared to non-smokers; the rest occur later in life when the loss of expectation of life is 7–8 years. There is, however, now clear evidence that stopping smoking before cancer or some other serious disease develops avoids most of the later risk of death from tobacco, even if cessation of smoking occurs in middle age (Table 7). While the rate at which young people start to smoke will be a major determinant of ill-health and mortality in the second half of this century, it is the extent to which current smokers give up the habit that will determine the mortality in the next few decades and which requires the urgent attention of public health authorities throughout Europe.

Tobacco smoke released into the environment by smokers, commonly referred to as environmental tobacco smoke (ETS) and which may be said to give rise to enforced 'passive smoking', has several deleterious effects on people who inhale it. It causes a small increase in the risk of lung cancer and also some increase in the risk of heart disease and respiratory disease, and is particularly harmful to small children. Smoking during pregnancy increases the risk of stillbirth, diminishes the infant's birth weight and impairs the child's subsequent mental and physical development, while smoking by either parent after the child's birth increases the child's risk of respiratory tract infection, severe asthma and sudden death.

Although the greatest hazard is caused by cigarette smoking, cigars can cause similar hazards if their smoke is inhaled, and both cigar and pipe smoking cause comparable hazards of cancers of the oral cavity, pharynx, extrinsic larynx and oesophagus. There is strong scientific evidence that smokeless tobacco, whether sucked, chewed or inhaled, is also associated with an increased risk of cancer.

Worldwide, it is estimated that smoking killed four million people each year in the 1990s, and that altogether some 60 million deaths were caused by tobacco in the second half of the twentieth century. In most countries, the worst consequences of the 'tobacco epidemic' are yet to emerge, particularly among women in developed countries and in the populations of developing countries, as, by the time the young smokers of today reach middle or

old age, there will be ~10 million deaths each year from tobacco (three million in the developed, seven million in the developing countries). If the current prevalence of smoking persists, ~500 million of the world's population today can expect to be killed by tobacco, 250 million in middle age.

The situation in Europe is particularly worrying. The European Union is the second largest producer of cigarettes (749 billion in 1997/98) after China (1675 billion in 1998) and the major exporter of cigarettes (400 billion). In Central and Eastern Europe, there has been a major increase in the smoking habit. Of the six World Health Organization (WHO) regions, Europe has the highest per capita consumption of manufactured cigarettes and faces an immediate and major challenge in meeting the WHO target for a minimum of 80% of the population to be non-smoking. In 1990–1994, 34% of men and 24% of women in the European Union were regular smokers. In women, the rates were reduced by the low rates in southern Europe, but the rates there are rising and seem set to continue to rise over the next decade. In the age range 25–39 years, the rates are higher (55% in men and 40% in women) and this can be expected to have a profound influence on the future incidence of disease. It is particularly disturbing that in many parts of Europe, the prevalence of smoking remains high among general practitioners, who should set an exemplary lifestyle in terms of health. This should be a target for immediate action.

It has been shown that changes in cigarette consumption are affected mainly at a sociological level rather than by actions targeted at individuals (for example, individual smoking cessation programmes). Actions such as advertising bans and increases in the price of cigarettes influence cigarette sales particularly among the young. A 'tobacco policy' is consequently essential to reduce the adverse health effects of tobacco, and experience shows that this should be aimed at both stopping young people from starting to smoke and helping smokers to stop. To be efficient and successful, a tobacco policy has to be comprehensive and maintained over a long time period. Increased taxes on tobacco, total bans on direct and indirect advertising, smoke-free enclosed public areas, prominent health warning labels on tobacco products, a policy of low maximum tar levels in cigarettes, education about the effects of smoking, encouragement of smoking cessation, and health interventions at the individual level, all need to be implemented. It must be recognised that nicotine is an addictive drug and that some smokers who are heavily addicted need medical help to overcome the addiction.

The importance of adequate intervention is shown by the low lung cancer rates in those Nordic countries which, since the early 1970s, have adopted integrated central and local policies and programmes against smoking. In the UK, tobacco consumption has declined by 46% since 1970 and lung cancer mortality among men has been decreasing since 1980, although the rate still remains high. In France, between 1993 and 1998, there has been a 11% reduction in tobacco consumption due to the implementation of antitobacco measures introduced by the Loi Evin.

The first point of the *European Code Against Cancer* is consequently:

Do not smoke. Smoking is the largest single cause of premature death.

If you smoke, stop doing so. In terms of health improvement, stopping smoking before having cancer or some other serious disease avoids most of the later excess risk of death from tobacco even if smoking is stopped in middle age.

If you fail to stop, do not smoke in the presence of non-smokers. The health consequences of your smoking may affect the health of those around you.

2. Avoid obesity.

3. Undertake some brisk, physical activity every day.

In this section, the adverse effect of obesity (or being overweight) and the protective effect of physical activity on cancer risk are summarised. It is based on the evidence from a comprehensive review on weight control and physical activity published by the International Agency for Research on Cancer (IARC). Because of the relationship between obesity and physical activity it is important to separate the effects of the two.

Obesity

Obesity is an established major cause of morbidity and mortality. It is the largest risk factor for chronic disease in western countries after smoking, particularly increasing the risk of diabetes, cardiovascular disease and cancer. Most countries in Europe have seen the prevalence of obesity [defined as a body mass index (BMI) of $\geq$30 kg/m^2; Figure 1] rapidly increase over the years. The prevalence ranges from <10% in France to ~20% in the UK and Germany and higher in some central European countries (>30%). It is associated with an increased risk of cancer at several sites and the evidence is clear for cancer of the colon, breast (postmenopausal), endometrium, kidney and oesophagus (adenocarcinoma). There is still an excess risk after allowing for several factors, such as physical activity. Overweight (BMI of 25–29 kg/m^2) is similarly associated with these cancers though the effect on risk is less.

The risk of colon cancer increases approximately linearly with increasing BMI between 23 and 30 kg/m^2. Compared with having a BMI <23 kg/m^2 the risk increases ~50–100% in people with a BMI $\geq$30 kg/m^2. The association appears to be greater in men than in women. For example, in the American Cancer Society cohort study of ~1.2 million people, the increase in risk of colon cancer in those with a BMI $\geq$30 kg/m^2 was 75% in men and 25% in women compared to those with a BMI <25 kg/m^2. The evidence also suggests that the risk does not depend on whether the person had been overweight in early adulthood or later in life.

Over 100 studies have consistently shown a modest increased risk of breast cancer in postmenopausal women with a high body weight. On average, epidemiological studies have shown an increase in breast cancer risk above a BMI of 24 kg/m^2. A pooled analysis of eight cohort studies of ~340 000 women showed an increase in risk of 30% in women with a BMI $\geq$28 kg/m^2 compared to those with a BMI of <21 kg/m^2. Factors that have been shown to attenuate the association between obesity and breast cancer include family history (heavier women with a family history of breast

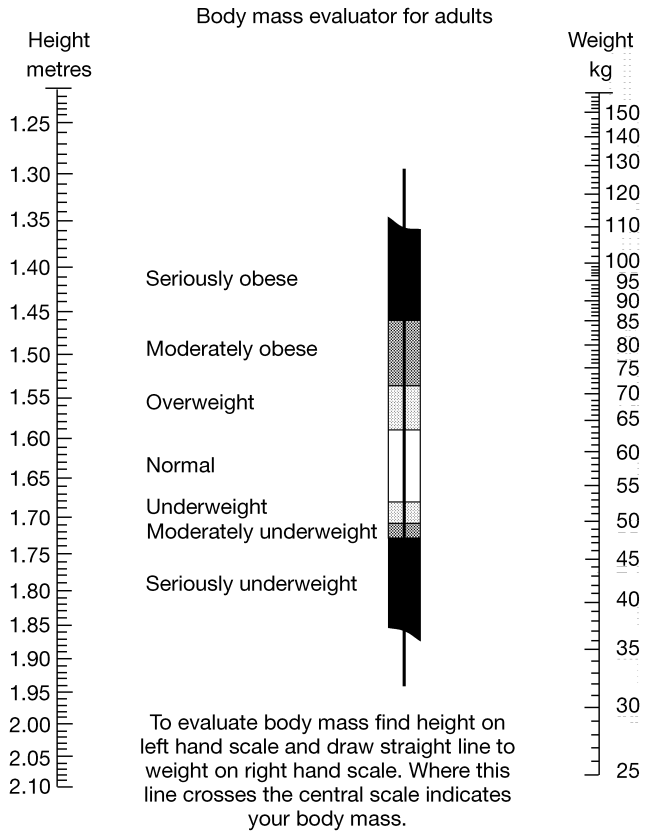

Figure 1. Calculation of body mass index from height and weight.

cancer have a higher risk than similar women without a family history) and the use of hormone replacement therapy (HRT) (the risk of breast cancer associated with obesity is greater in women who had never used HRT). In contrast, among premenopausal women obesity is not associated with an increase in risk of breast cancer.

There is consistent evidence that being overweight is associated with an increased risk of endometrial cancer. Women with a BMI of >25 kg/m^2 have a two- to three-fold increase in risk. Although limited, the evidence suggests that the risk is similar in pre- and postmenopausal women. There is evidence that the risk is greater for upper-body obesity.

The association between kidney (renal cell) cancer and BMI is also well established and is independent of blood pressure. Individuals with a BMI of ≥30 kg/m^2 have a two- to three-fold increase in risk compared with those below 25 kg/m^2. The effect is similar in men and women. There is a similarly strong association between being overweight and adenocarcinoma of the lower oesophagus and the gastric cardia; about two-fold increase in risk in individuals with a BMI of >25 kg/m^2. A modest association has been reported in a pooled analysis of BMI and thyroid cancer (the increase in risk in those in the highest third of BMI was 20% in women and 50% in men). The evidence on obesity and gallbladder cancer is limited but there is a suggestion of almost a two-fold increase in risk, especially in women.

In Western Europe, it has been estimated that being overweight or obese accounts for ~11% of all colon cancers, 9% of breast cancers, 39% of endometrial cancers, 37% of oesophageal adenocarcinomas, 25% of renal cell cancer and 24% of gallbladder cancer.

Physical activity

Many studies have examined the relationship between physical activity and the risk of developing cancer. There is consistent evidence that some form of regular physical activity is associated with a reduction in the risk of colon cancer. There is also a suggestion of a risk reduction in relation to cancer of the breast, endometrium and prostate. The protective effect of physical activity on cancer risk improves with increasing levels of activity (the more the better) though such a recommendation should be moderated in individuals with cardiovascular disease. Regular physical activity that involves some exertion may be needed to maintain a healthy body weight, particularly for people with sedentary lifestyles. This could involve half an hour per day three times per week. More vigorous activity several times per week may give some additional benefits regarding cancer prevention.

For some cancers, the preventive effect of regular physical activity seems to act independently of weight control. The prevention of weight gain and obesity and the promotion of exercise should ideally begin early in life. However, the benefits can also be gained later in life if a healthy lifestyle is adopted. It is desirable to maintain a BMI in the range of 18.5–25 kg/m^2, and people who are already overweight or obese should aim to reduce their BMI to <25 kg/m^2. A lifestyle that incorporates a healthy diet, exercise and weight control is beneficial to the individual not only with regards to cancer but also other diseases.

4. Increase your daily intake and variety of vegetables and fruits: eat at least five servings daily. Limit your intake of foods containing fats from animal sources.

Diet and nutritional factors started to be the focus of serious attention in the aetiology of cancer from the 1940s onwards. Originally dealing with the effect of feeding specific diets to animals receiving chemical carcinogens, research turned to the potential of associations with human cancer risk. Initially, this was conducted through international comparisons of estimated national per capita food intake data with cancer mortality rates. It was consistently found that there were very strong correlations in these data, particularly with dietary fat intake and breast cancer. As dietary assessment methods became better, and certain methodological difficulties were identified and overcome, the science of Nutritional Epidemiology emerged.

Doll and Peto estimated that somewhere between 10 and 70% of all cancer deaths were associated with dietary and nutritional practices, with the best estimate ~30%. In 1983, the United States Academy of Science concluded that, after tobacco smoking, diet and nutrition was the single most important cause of cancer. Since then, the epidemiological search has been to improve knowledge of the exact relationships between food and nutrition and cancer risk and to identify associations with particular components of diet and determine the best intervention strategy.

Initially, much attention focused on intake of fat in the diet, particularly from animal sources. Although the results from ecological studies and data from animal experiments were very strong regarding this association, findings from retrospective and prospective epidemiological studies have been inconsistent, particularly regarding the association with breast cancer and colorectal cancers.

A number of epidemiological studies indicate a protective effect of higher intakes of vegetables and fruit on the risk of a wide variety of cancers, in particular oesophagus, stomach, colon, rectum and pancreas. A higher consumption of vegetables and fruits has been associated with a reduced risk of cancer at various sites in several studies from Europe, mostly using a case–control design. The relation is however less consistent in data from several cohort studies from North America. If any, the association was apparently most marked for epithelial cancers, in particular those of the alimentary and respiratory tract, although such an association is weak to non-existent for hormone-related cancers.

Cereals with high fibre content and whole-grain cereals have been associated with lower risk of colorectal cancer and other digestive tract tumours in a few European studies. However, several large cohort and randomised intervention studies have not supported this association. The EPIC (European Prospective Investigation into Cancer and Nutrition) study, examined this association in 519978 individuals aged 25–70 years, recruited from 10 European countries. Follow-up consisted of 1939011 person-years, and data for 1065 reported cases of colorectal cancer were included in the analysis. Dietary fibre in foods was inversely related to incidence of large bowel cancer {adjusted relative risk 0.75 [95% confidence interval (CI) 0.59–0.95] for the highest versus lowest quintile of intake}, the protective effect being greatest for the left side of the colon, and least for the rectum. After calibration with more detailed dietary data, the adjusted relative risk for the highest versus lowest quintile of fibre from food intake was 0.58 (95% CI 0.41–0.85). No food source of fibre was significantly more protective than others, and non-food supplement sources of fibre were not investigated. The authors concluded that in populations with low average intake of dietary fibre, an approximate doubling of total fibre intake from foods could reduce the risk of colorectal cancer by 40%.

The confusing nature of this association between fibre intake and colorectal cancer risk is highlighted by the simultaneous publication of two studies, one of which confirmed this finding and another which reported no association.

Lower rates of many forms of cancer reported in southern European regions, like in Southern Europe, have been attributed to a diet lower in meats and fats from animal sources, and higher in fish, olive oil, vegetables and fruits, grains and moderate alcohol consumption. While a link has been suggested, this has not yet been proved convincingly.

The association with reduced risk of cancer exists for a wide variety of vegetables and fruits. There also exists increasing evidence that consumption of higher levels is also beneficial for other chronic diseases. Vegetables and fruits contain a large number of potentially anticarcinogenic agents, with complementary and overlapping mechanisms of action. However, the exact molecule(s) in vegetables and fruits that confers this protection is unknown. Insight into the mechanisms of action is only incomplete, but this is not required for public health recommendations. It is, in any case, not possible to recommend dietary supplementation with vitamins and minerals to reduce cancer risk based on the evidence currently available.

Nonetheless, it is difficult to be precise about the advisable quantity of fruits and vegetables and it is difficult to imagine the successful implementation of a randomised trial of increased consumption of fruits and vegetables. The best available evidence comes from observational studies and the search continues for the molecule(s) in fruits and vegetables responsible for the apparent protection.

Fruits and vegetables should be taken with each meal whenever possible, and systematically replace snacks between meals. In line with WHO and USA recommendations, ‘five-a-day’ (minimum 400 g/day, i.e. two pieces of fruit and 200 g of vegetables) is advocated, which could lead to a reduction in cancer risk. Particular attention regarding changing nutritional practices needs to be paid to the countries of central and Eastern Europe, where rapid changes in dietary patterns have been shown to have had a rapid positive influence on death rates from chronic disease.

5. If you drink alcohol, whether beer, wine or spirits, moderate your consumption to two drinks per day if you are a man or one drink per day if you are a woman.

There is wide variability among European Union countries in terms of per capita average alcohol consumption and preferred type of alcoholic beverage (Figure 2). Although three groups of countries are traditionally identified according to the prevalent drinking culture (wine drinking in the South, beer drinking in the Central Europe and spirit drinking in the North), there is considerable variability within such groups and within countries, and new patterns are evolving rapidly (e.g. increasing consumption of wine in northern countries; increasing prevalence of binge drinking, in particular among women).

There is convincing epidemiological evidence that the consumption of alcoholic beverages increases the risk of cancers of the oral cavity, pharynx and larynx and of squamous cell carcinoma of the oesophagus. The risks tend to increase with the amount of ethanol drunk, in the absence of any clearly defined threshold below which no effect is evident.

Although alcohol drinking increases the risk of upper digestive and respiratory tract neoplasms, even in the absence of smoking, alcohol drinking and tobacco smoking together greatly increase the risk of these cancers, each factor approximately multiplying the effect of the other. Compared to never-smokers and non-alcohol drinkers, the relative risk of these neoplasms is increased between 10- and 100-fold in people who drink and smoke heavily (Figure 3). Indeed, in the case of total abstinence from drinking and smoking, the risk of oral, pharyngeal, laryngeal and squamous cell oesophageal cancers in European countries would have been extremely low.

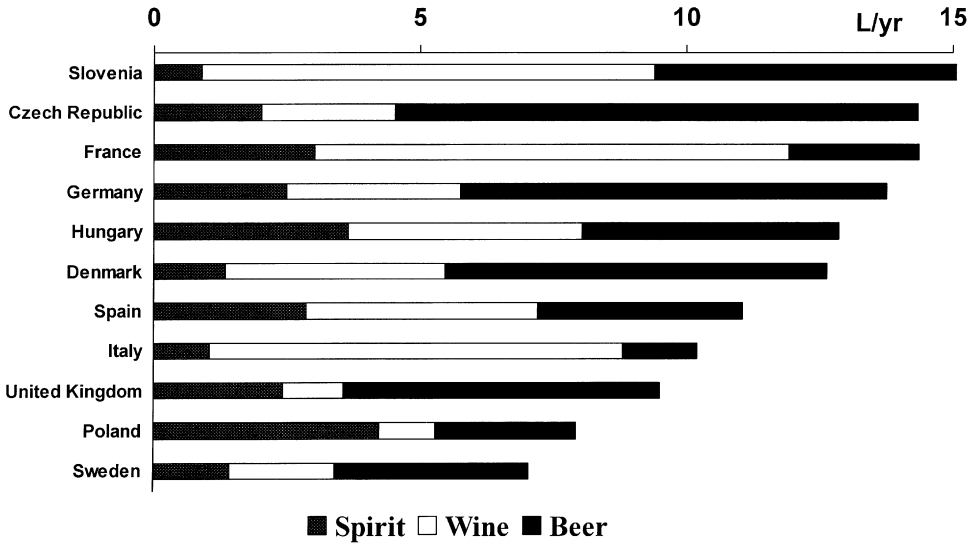

Figure 2. Recorded per capita alcohol consumption among adults in selected European Union and accession countries, by type of beverage (1996).

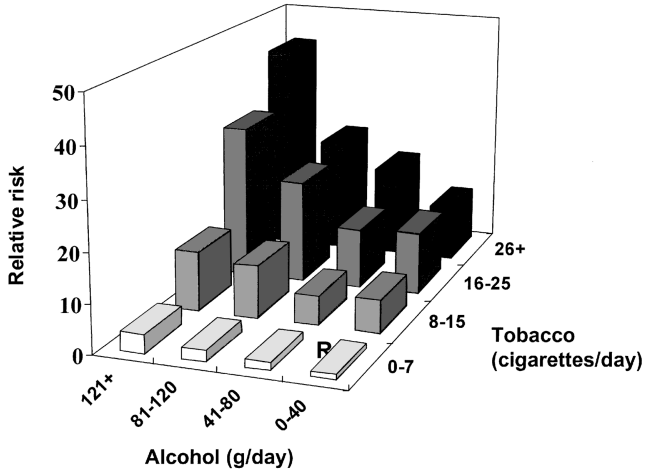

Figure 3. Relative risk of laryngeal cancer for tobacco smoking and alcohol drinking in a study from Southern Europe. Ref, reference category (risk = 1).

A likely carcinogenic mechanism of alcohol is by facilitating the carcinogenic effect of tobacco and possibly of other carcinogens to which the upper digestive and respiratory tract are exposed, particularly those of dietary origin. However, a direct carcinogenic effect of acetaldehyde, the main metabolite of ethanol, and of other agents present in alcoholic beverages cannot be excluded. A diet poor in fruits and vegetables, typical of heavy drinkers, is also likely to play an important role. There does not seem to be a different effect of beer, wine or spirits on cancer risk at these sites; rather the total amount of ethanol ingested appears to be the key factor in determining the increase in risk. Only a few studies have analysed the relationship between stopping alcohol drinking and the risk of cancers of the upper respiratory and digestive tract. There is clear evidence that the risk of oesophageal cancer is reduced by 60% 10 years or more after drinking cessation. The pattern of risk is less clear for oral and laryngeal cancers. Stopping (or reducing) alcohol drinking, particularly in association with smoking cessation, represents a priority for preventing oesophageal cancer.

Alcohol drinking is also strongly associated with the risk of primary liver cancer; the mechanism however might be mainly or solely via the development of liver cirrhosis, implying that light or moderate drinking may have limited influence on liver cancer risk. Moreover, there is some evidence suggesting that heavy alcohol consumption is particularly strongly associated with liver cancer among smokers and among people chronically infected with hepatitis C virus (HCV).

An increased risk of colorectal cancer has been observed in many cohort and case–control studies, which seems to be linearly correlated with the amount of alcohol consumed and independent from the type of beverage.

An increased risk of breast cancer has been consistently reported in epidemiological studies conducted in different populations. Although not strong (increased risk in the order of 10% for each 10 g/day increase in alcohol intake, possibly reaching a plateau at the highest levels of intake), the association is of great importance because of the apparent lack of a threshold, the large number of women drinking a small amount of alcohol and the high incidence of the disease. Indeed, more cases of breast cancer than of any other cancer are attributable to alcohol drinking among European women (Table 8). It has been suggested that alcohol acts on hormonal factors involved in breast carcinogenesis, but the evidence is currently inadequate to identify a specific mechanism.

Besides increasing cancer risk, alcohol drinking entails complex health consequences, making it difficult to formulate universal public health guidelines. There is strong evidence for a J-shaped pattern of risk of total mortality and cardiovascular disease according to increasing alcohol consumption (Figure 4). This classic pattern is one of decreased risk in light drinkers compared with non-drinkers and then an increasing risk as alcohol consumption increases. In addition, alcohol drinking increases the risk of injuries in many types of motor vehicle, leisure and occupational injuries (e.g. driving, swimming, manual working) and accident mortality rates are influenced by per capita alcohol consumption across Europe. Moreover, drinking alcohol during pregnancy has a detrimental effect on the development of the foetus and its

Table 8. Estimated number and proportion of cancer cases attributable to alcohol consumption in European Union (1995)

Cancer	Men		Women	
	n	%	*n*	%
Oral Cavity and Pharynx	13 900	36	2700	29
Oesophagus	7400	41	2100	34
Liver	3300	17	500	25
Larynx	6600	30	1200	13
Breast			6000	3

Sources: All information taken from Pisani P. Avoidable Cancer in Europe: Estimating Etiologic Fractions. Final Report to the European Commission, Contract No. 96-200504. Lyon, France: International Agency for Research on Cancer 2000. The exception is breast cancer, which was calculated based on a relative risk of 1.1 and prevalence of exposure of 30%.

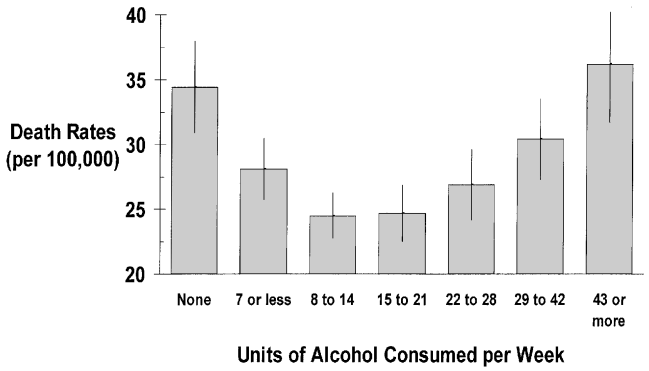

Figure 4. Annual mortality by alcohol consumption for all causes of death in men. One unit of alcohol (a glass of beer, wine or spirits) corresponds to 8–10 g of ethanol. Source: Doll R, Peto R, Hall E et al. Mortality in relation to consumption of alcohol: 13 years' observations on male British doctors. BMJ 1994; 309: 911–918.

central nervous sytem, often resulting in malformations, behavioural disorders and cognitive deficits in the postnatal period.

For these reasons, the task of fixing a threshold on daily alcohol intake below which the increased risk of cancer and other diseases is offset by a reduced risk of cardiovascular diseases is not simple. Factors such as age, physiological condition and dietary intake certainly modify any such threshold: in particular, the beneficial effects on cardiovascular diseases appear only at middle age.

In conclusion, there is evidence showing that a daily alcohol intake as low as 10 g/day (that is, approximately, one can of beer, one glass of wine or one shot of spirit) (Figure 5) is associated with some increase in breast cancer risk relative to non-drinkers, while the intake associated with a significant risk of cancer at other sites (such as cancers of the upper digestive and respiratory tracts, liver or colorectum) is probably somewhat higher (~20–30 g/day).

All the above points should be considered to give sensible advice regarding individual recommended limits of alcohol consumption. The limit should not exceed between 20 g of ethanol per day (i.e. approximately two drinks of either beer, wine or spirit each day) and it should be as low as 10 g per day for women.

Figure 5. One unit of alcohol. From left to right: a glass of wine, a glass of beer, and a shot of whisky.

6. Care must be taken to avoid excessive sun exposure. It is specifically important to protect children and adolescents. For individuals who have a tendency to burn in the sun active protective measures must be taken throughout life.

Skin cancer is predominantly, but not exclusively, a disease of white skinned people. Its incidence, furthermore, is greatest where fair skinned peoples live at increased exposure to ultraviolet (UV) light, such as in Australia. Figure 6 shows the marked latitudinal gradient in age-related incidence of melanoma, the form of skin cancer most likely to metastasise and cause death. The main environmental cause of skin cancers is sun exposure, and UV light is deemed to represent the component of the solar spectrum involved in skin cancer occurrence.

The type of sun exposure which causes skin cancer however appears to differ in the three main types. Squamous cell carcinoma shows the clearest relationship with cumulative sun exposure. This form of skin cancer is therefore most common in outdoor workers. The recipients of transplanted organs are particularly at risk of these tumours as a result of the combined effects of the unchecked growth of human papilloma virus (HPV) in their skin due to immunosuppression, and exposure to the sun. Basal cell carcinoma is the commonest type of skin cancer but it is the least serious as it is a local disease only. This form of skin cancer appears to share an aetiological relationship to sun exposure with melanoma.

The risk of cutaneous melanoma appears to be related to intermittent sun exposure. Examples of intermittent sun exposure are sunbathing activities and outdoor sport activities. Also, a history of sunburn has repeatedly been described as a risk factor for melanoma, which again is associated with intermittent sun exposure.

The incidence of melanoma has doubled in Europe between the 1960s and the 1990s and this is attributed to increased intense sun

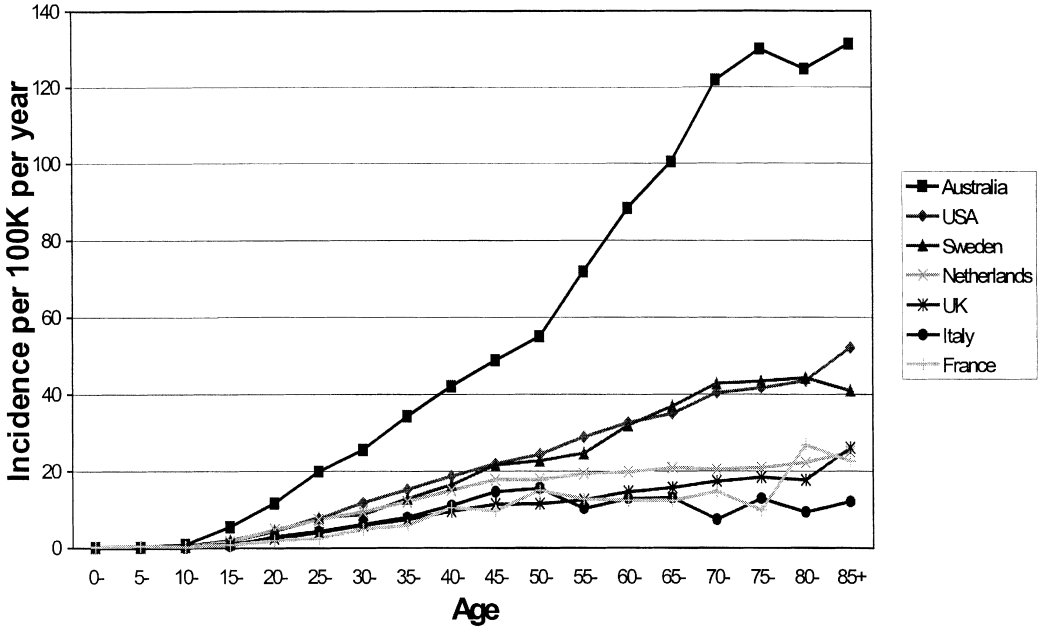

Figure 6. Age-specific incidence of melanoma in various countries.

exposure, which has taken place this century. The incidence of squamous cell and of basal cell cancers has also increased in all European countries. Although much less life threatening than melanoma, these tumours represent 95% of all skin cancers, and their treatment amount to considerable costs for individuals and social security systems.

The advice to the European population must therefore be to moderate sun exposure: to reduce their total life-time exposure, and in particular to avoid extremes of sun exposure and sunburn. All Europeans however are not equally susceptible to skin cancer. The fairest are more susceptible, particularly those with red hair (but not exclusively), freckles and a tendency to burn in the sun.

The strongest phenotypic risk factor for melanoma however is the presence of large numbers of moles or melanocytic naevi, and twin study evidence is strong that the major determinant of naevus number is genetic with an added contribution from sun exposure. These naevi may be normal in appearance but are also usually accompanied by so-called atypical moles: moles which are larger than 5 mm in diameter with variable colour within and an irregular shape. The phenotype is described as atypical mole syndrome (AMS). The AMS is present in something like 2% of the north European population and is associated with an approximately ten times increased risk of melanoma. Advice about sun protection is therefore particularly of importance to this sector of the population. Some patients with the AMS report a family history, and overall a strong (three or more cases) family history is the greatest predictor of risk. These families should avoid the sun and should be referred to dermatologists for counselling.

The best protection from the summer sun is to stay out of it, but the following advice is given in order to allow safer enjoyment of the outdoors. Keeping out of the sun between 11 am and 3 pm is effective as UV exposure is greatest at this time. Therefore, scheduling outdoor activities for other times is important, particularly for children. Using shade is allied to this and clothing remains the second most important measure. Close weave heavy cotton affords good protection although the clothing industry is increasingly developing UV protective clothes with high sun protection properties, which are very valuable particularly where it is difficult to keep out of the sun.

Sunscreens are useful for protection against sunburns of skin sites such as the face and the ears. Sunscreen may protect against squamous cell carcinoma but there is currently inadequate evidence for their preventive effect against basal cell carcinoma and melanoma. However it is extremely important when using sunscreen to avoid prolongation of the duration of sun exposure that may be responsible for an increased risk of melanoma. Additionally, there is evidence that using higher SPF sunscreen prolongs further time spent in the sun. Great care should be taken when choosing to use sunscreen and also in the choice of SPF. In addition, sunbed use is also discouraged, as exposure to these devices resembles the type of sun exposure mostly associated with melanoma occurrence.

7. Apply strictly regulations aimed at preventing any exposure to known cancer-causing substances. Follow all health and safety instructions on substances which may cause cancer. Follow advice of national radiation protection offices.

The prevention of exposure to occupational and environmental carcinogens has followed the identification of a substantial number of natural and man-made carcinogens, and has led to significant reductions in cancer occurrence. The message in this item of the code solicits responsible behaviour for individuals in three respects: (i) from those who have to provide timely and clear instructions, primarily legislators and regulators who should adapt

scientific consensus evaluations into European Union law, and control compliance with these regulations; (ii) from those who should follow these instructions and comply with the laws to protect the health of others, for instance, managers, hygienists and doctors in industry; and (iii) from every citizen who in order to protect their own health and the health of others, ought to pay heed to the presence of carcinogenic pollutants and follow instructions and regulations aimed at mitigating or preventing exposure to carcinogens. The latter applies to a wide variety of circumstances such as traffic restrictions within cities, restrictions on smoking, use of personal safety devices and respecting validated procedures in the workplace. Application of regulations is particularly important in the working environment where carcinogens may be found in higher concentrations than in the general environment. The control of the prevalence and level of exposure to occupational and environmental carcinogens through general preventive measures has historically played a more important role in preventing cancers than individual measures of protection.

The cancers that have most frequently been associated with occupational exposures are those of the lung, urinary bladder, mesothelioma, larynx, leukaemia, angiosarcoma of the liver, nose and nasal cavity and skin (non-melanoma). Several other neoplasms have also been associated with occupational exposures but the evidence is less strong. They include cancers of the oral cavity, nasopharynx, oesophagus, stomach, colon and rectum, pancreas, breast, testis, kidney, prostate, brain, bones, soft-tissue sarcoma, lymphomas and multiple myeloma. Most known or suspected occupational carcinogens have been evaluated by the IARC (Lyon, France). Actually, 29 chemical or physical agents, groups of agents or mixtures that occur predominantly in the workplace, have been classified as human carcinogens (Group 1 of the IARC classification). In the same Group 1, IARC has classified 13 industrial processes or occupations, such as the rubber industry, painters, etc. In European Union countries, production or use of some of these chemicals has been banned and are only of historical interest (e.g. mustard gas, 2-naphthylamine), while some high-risk industries have stopped functioning (e.g. 'Wismut' uranium ore mining associated with exposure to ionising radiation). Exposure to other carcinogens such as metals and dioxins is still widespread.

Thirty-five agents or industrial processes are classified as probably carcinogenic to humans (Group 2A of the IARC). Many of the agents in this group are still widely used, for example 1,3-butadiene and formaldehyde. More than 200 agents, groups of agents or exposure circumstances are classified as possibly carcinogenic to humans (Group 2B) largely on the basis of carcinogenicity data from animal experiments. It has been estimated that in the early 1990s about 32 million workers (23% of those employed) in the European Union were exposed to carcinogenic agents at levels above background. Exposure to these agents is still widespread but occurs mostly at low levels. The more common occupational exposures are solar radiation, passive smoking, crystalline silica, diesel exhaust, radon, wood dust, benzene, asbestos, formaldehyde, polycyclic aromatic hydrocarbons, chromium VI, cadmium and nickel compounds.

Extensive preventive measures in the workplace in recent decades have resulted in the prevention of many cancers related to workplace exposures. This has been well documented, for example for occupational bladder cancer after the ban on the use of β-naphthylamine in the rubber and chemical industries. The delays in taking protective measures, however, and the long latency for many neoplasms will result, in certain instances, in a continuous increase in the number of occupational cancers during the coming years. An increasing number of mesothelioma cases due to past occupational exposure to asbestos is expected in many European Union countries for another 10–20 years, even though asbestos has been banned in some European Union countries since the early 1990s. The proportion of all cancers that can be causally attributed to carcinogens in the occupational environment and are therefore wholly or partially avoidable through exposure control, remains difficult to quantify reliably. An estimated 5% of cancers is attributable to the occupational environment. This proportion depends on the variable prevalence of the exposures by geographical areas, gender, socioeconomic status and periods of time, as well as on the concurrent prevalence of other dominant cancer causing factors, particularly tobacco smoking. Furthermore, the effect of specific occupational carcinogens, such as aromatic amines or polycyclic aromatic hydrocarbons, is also mediated by genetic factors, such as genetic polymorphisms of the NAT2 or GSTM1 genes. The distribution of these polymorphisms within the populations of the European Union is fairly uniform and genetic factors probably do not determine differences in the proportion of occupational cancers between populations in European Union countries.

Environmental exposures usually refer to exposures of the general population that cannot be directly controlled by the individual. They include air-pollution, drinking water contaminants, passive smoking, radon in buildings, exposure to solar radiation, food contaminants such as pesticide residues, dioxins or environmental estrogens, chemicals from industrial emissions, and others. Exposure may be widespread, as is the case for air pollution, or could be restricted, as would be the case of populations living in the vicinity of a contaminating industry. These exposures have been associated with a variety of neoplasms, including cancers of the lung, urinary bladder, leukaemia and skin. The impact of several environmental carcinogenic exposures, such as arsenic in drinking water, has not been quantified, though exposure to arsenic is likely to affect only limited population groups. Air pollutants, such as fine particles, have been associated in several studies with a small increased risk of lung cancer even at current low-level urban exposure levels. The evidence on other exposures that are widespread, such as disinfection by-products in drinking water, is still inconclusive. Agents in the general environment to which a large number of subjects are exposed for long periods, such as passive smoking or air-pollution, although increasing only modestly the relative risk for certain cancers may be at the origin of several thousand cases per year in the European Union.

It is essential that for any agent liable to present a risk, the nature, degree and duration of such risk must be determined in order to define what measures need to be taken to prevent or reduce the exposure. Among these measures, suitable operating

Table 9. Sources of ionising radiation to man

Source	Worldwide average annual effective dose[a], millisievert (mSv)
Natural background	2.4
Diagnostic medical examinations	0.3
Atmospheric nuclear testing	0.005
Chernobyl accident	0.002
Nuclear power production	0.001

[a]Average radiation doses for 2000 from natural and man-made sources of radiation.
Source: UNSCEAR, 49th session, Vienna, 2–11 May 2000, www.unscear.org/press_releases.htm (23 March 2003, date last accessed).

procedures and methods are of utmost importance. Instructions to be followed may take the form of quantitative control limits of exposure, derived empirically or through formal procedures, which still leaves much to be desired. The specification of a quantitative control limit of exposure in the general and occupational environment combines two elements: the quantitative estimate of the risk associated with a given level of exposure and the level of risk regarded as socially 'acceptable', with consideration of the technical feasibility, and human and economic costs of various degrees of control.

Ionising and non-ionising radiation

Ionising radiation at high doses causes cancer in humans: only a few cancer types have never been related to ionising radiation. This has been known for decades, and excellent summaries of the scientific literature are available. The IARC recently classified X-rays, γ-rays and neutrons as carcinogenic to humans (Group 1). This is irrespective of the different patterns of energy release and penetrating power of the different types of ionising radiation. Energy at high levels may lead to cellular and DNA damage followed by cell killing, whereas at lower doses it may lead to mutations increasing the risk of cancer. The International Commission on Radiological Protection (ICRP) issues recommendations for radiological protection based on the existing scientific literature.

High-dose ionising radiation is used in medicine to treat cancer. These types of exposures are at present outside the scope of the *European Code Against Cancer*. However, much of our evidence on the effects of ionising radiation on humans is derived from such uses, and from the atomic bomb survivors at Hiroshima and Nagasaki. The main source of radiation to the human population comes from the natural background, both terrestrial and cosmic (Table 9), whilst the man-made sources, such as atmospheric nuclear testing, nuclear accidents (e.g. Chernobyl) and nuclear power production, which cause the most public concern, cause only very little exposure (Table 9).

The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) estimates the population risk of dying from cancer after an acute dose of 1000 mSv is about 9% for men and 13% for women. The estimates could be reduced by 50% for chronic exposures. The worldwide average annual effective dose is 2.4 mSv. The lifetime exposure of the population to all sources of ionising radiation was estimated by the National Radiological Protection Board to account for 1% of all fatal cancers in the UK (http://www.nrpb.org/radiation_topics/risks/cancer_risk.htm, 22 November 2002). Only 1% of this risk is ascribed to the small doses from man-made radiation.

For the purpose of the *European Code Against Cancer*, this review concentrates on the possible effects of the natural background radiation, terrestrial (in the form of radon gas) and cosmic radiation, as it is possible to control exposure to both. Furthermore, we assess the cancer risk related to the Chernobyl accident and that among nuclear workers and people living near nuclear installations. Diagnostic radiation is of concern for the population groups undergoing examinations, be it screening of healthy individuals with mammography or computed tomography (CT) scans for lung cancer or when there is a suspicion of thyroid disease. Screening with low-dose CT for lung cancer is reported to give an effective dose of between 0.2 and 1 mSv. Using the risk factor of 5% per 1 Sv (ICRP 60), this would imply one to five radiation induced fatal cancers per 100 000 examinations. Mammography screening for breast cancer typically gives an absorbed average glandular dose of 3 mGy. It has been estimated in Sweden that among women aged 50–69 years, with a reduction in breast cancer mortality due to a mammographic screening programme of 25%, that 560 deaths from breast cancer would be avoided. It is estimated that the effect of the radiation would be to induce between 1 and 5 fatal breast cancers per 100 000 examinations. Although the collective dose from diagnostics to the population is small relative to natural radiation, benefit analyses should be performed to avoid unnecessary exposure.

Non-ionising radiation from sources such as power lines, electrical equipment, mobile phones and solar radiation raise public concern as to a possible carcinogenic effect. The ICNIRP (International Commission on Non-ionising Radiation Protection) issues guidelines for limiting exposure, and the German Stralenschutzkommission and the UK NRPB recently published reviews assessing the health risks. The evidence on power lines and mobile phones are dealt with in this section, whereas solar radiation is dealt with separately.

Radon and cancer. Radon-222 is a naturally occurring chemically inert gas, which arises from the decay chain of uranium in the earth's crust. Inhalation of air containing radon and its products results in the exposure of cells in the bronchial epithelium and elsewhere to ionising radiation, chiefly from α-particles. Surveys have indicated that radon accounts for an average annual effective dose of 1.15 mSv worldwide, almost half the total annual effective dose from all natural sources of radiation. There is very wide variation in levels of radon exposure and a number of populations are exposed to levels that are more than a factor of ten higher than the overall average. The majority of exposure to radon occurs indoors, especially in homes, where the principal source is usually the subsoil, although under some circumstances appreciable exposure may occur from building materials or from radon dissolved in water.

There is conclusive evidence from studies of underground miners occupationally exposed to high concentrations of radon in air that radon is a cause of lung cancer. Extrapolation from the miners' studies to the likely effects of environmental exposure to radon suggests that radon should be the second most important cause of lung cancer in the general population after cigarette smoking, and that the majority of radon-induced lung cancers are in those who smoke cigarettes or who have smoked them in the past. Direct studies of the risk of lung cancer from residential radon exposure are consistent with these conclusions. The studies of underground miners and also some direct studies suggest that high concentrations of radon in air do not cause a material risk of death from cancers other than lung cancer.

When a new house or other building is being constructed, it is usually possible, for a minimal cost, to ensure that the radon concentration inside the building will be very low. For existing buildings it is also usually possible at some cost to reduce the radon concentrations. In terms of risk reduction, such measures will have their biggest effect on smoking inhabitants.

Cosmic radiation and cancer. Recently, several epidemiological studies have been carried out to investigate cancer mortality and cancer incidence among airline crew. Many exposure studies have been conducted to estimate and to measure the dose of cosmic radiation at flight altitudes of jet aircraft. The latter studies conclude that a typical annual radiation dose is between 3 and 6 mSv for a commercial pilot. Values up to 9 mSv have been estimated for a pilot flying some 600 h/year on polar flights at 10 km and above. Detailed assessment of individual flight history has showed that for all pilots the lifetime cumulative exposure was below 100 mSv. Results of the mortality studies and incidence studies are as yet inconclusive, although for most cohorts the total cancer (mortality and incidence) was not raised compared with the general population. For specific cancer sites, increased and decreased standardised mortality or incidence ratios were observed without a clear pattern. Leukaemia risk is not increased, with the exception of a study of Danish pilots, based on only 14 cases. A more consistent finding is an increased risk of breast cancer, which is also a cancer associated with radiation. The role of risk factors other than radiation, such as late first childbirth and low parity, may not always have been fully taken into account when evaluating these findings. Another consistent finding is an increase in skin cancer and melanoma. Whether this is related to leisure activities, occupational factors or a combination of both needs further investigation.

The overwhelming evidence does not point to a significant adverse health effect in terms of cancer, and the present regulation of aircrew as radiation workers sufficiently controls the occupational exposure. Very few passengers will ever accumulate radiation doses from cosmic radiation in the same magnitude as the staff and hence no particular precautions need to be taken.

Radioiodine and thyroid cancer. Ionising radiation is the only definitely established cause of thyroid cancer in humans, although only a small proportion of thyroid cancers can be accounted for by radiation. The thyroid gland is highly susceptible to ionising radiation presumably because of its superficial location, high level of oxygenation, and high cell turnover rate. A pooled analysis of seven studies revealed that thyroid cancer was induced even by low doses of brief external γ-radiation in childhood, but rarely developed after exposure in adulthood. Data from the atomic bomb survivors underline the strong modifying effect of age at exposure, with no excess risk seen in individuals older than 20 years. During the first 14 years after the Chernobyl accident, ~1800 thyroid cancers were diagnosed in the three most contaminated countries among children younger than 15 years, whereas only three or four childhood thyroid cancers were registered annually in the same area before the accident. No increased thyroid cancer as a consequence of the Chernobyl accident has been identified in adults.

The major concern regarding medical use of ionising radiation has been the possibility that thyroid examinations or treatments using radioiodine cause thyroid cancer. The annual number of thyroid examinations using radioiodine is currently five per 1000 individuals in the western world. Patients treated with ^{131}I for hyperthyroidism are almost entirely adults and no increased risk of thyroid cancer is seen among these patients. It is also likely that the doses, ranging from 100 to 300 Gy, received by the thyroid gland induce cell killing instead of carcinogenic transformation.

Nuclear workers. Many studies have been carried out of cancer among nuclear industry workers. Most of the exposures to these workers were in line with international standards. In contrast, many workers at the Mayak plant in Russia received high doses over a protracted period, and raised (but poorly quantified) risks have been seen for several types of cancer in this group. Some of the worker studies have been limited by relatively small population sizes and/or short follow-up periods. The larger studies include a combined analysis of ~95 000 workers in Canada, the US and the UK, and cohorts of >100 000 nuclear workers in Japan (although with a short follow-up) and the UK. Most of the analyses have looked only at mortality. There has been some variation in the findings, which may be due in part to low statistical precision. However, mortality has often been lower than in the general population, due probably to factors associated with selection into and continuation of employment. The larger studies have tended to indicate an increasing trend in leukaemia risk with increasing dose, whereas the evidence for a dose-related increase in solid tumour risks has generally been less. However, the confidence limits for these trend estimates have been relatively wide, and encompass risks extrapolated from the Japanese atomic-bomb survivors as well as a range of values, both higher and lower. More precise information will be obtained from an ongoing international collaborative study of cancer risk in nuclear industry workers.

At present, the findings from these studies do not indicate the need to modify current radiation protection measures for workers.

Populations living near nuclear installations. Various studies have been carried out of cancer rates in the vicinity of nuclear installations in recent years, mostly in Western Europe and North America. Doses to populations around these installations were

generally several orders of magnitude lower than those to persons living near the Techa River in Russia at the time of high discharges from the Mayak plant. There is evidence of raised cancer risks in this latter group, although quantification is difficult.

There does not appear to have been a general increase in rates of adult cancers around nuclear installations. Some, but not all, studies have indicated increased rates of childhood cancers and particularly childhood leukaemia. The evidence for such increases has tended to be strongest in the vicinity of nuclear reprocessing plants; in particular, Sellafield and Dounreay in the UK and, to a lesser extent, La Hague in France. Interpretation of these studies has been hindered in part by small numbers of cases and by the ecological (correlation) study design used in many instances. Assessments of radiation doses to those living near these installations do not suggest that the raised childhood leukaemia risks can be explained on the basis of radioactive discharges. Case–control studies generally do not demonstrate clear links with habits that might give rise to enhanced environmental exposures. A case–control study around Sellafield suggested a link between childhood leukaemia and paternal occupational radiation exposure prior to conception. However, this has not been replicated in larger studies elsewhere, and may have been a chance finding. Non-radiation factors such as population mixing have been mentioned as possible explanations for the raised risks, but it is unclear whether these factors could explain all the results.

At present, specific actions are not indicated over and above existing guidelines on radiation exposures to members of the public. However, continued monitoring of environmental radioactivity and cancer rates around nuclear installations is desirable.

Power lines and cancer. Power lines produce extremely low frequency (ELF) electromagnetic fields in range of 50–60 Hz. Electric fields do not reach people inside houses, but magnetic fields go through most materials and cause an additional exposure higher than the typical background field (about 0.1 μT) up to a distance ~50 metres from the power line, depending on the voltage and wire configuration. Health effects on humans related to this non-ionising type of radiation have been investigated in epidemiological studies for over two decades.

The first report of an association between childhood cancer and power line exposure was published in 1979, and after that at least 24 studies on the same topic have been published. There have been two meta-analyses published lately that both suggest a significant 1.7–2.0-fold excess of childhood leukaemia in the extremely rarely existing fields above 0.3 or 0.4 μT. The excess may be attributable to patient selection and publication bias, and a plausible biological mechanism is not known.

It appears on the basis of studies with large numbers of cancer cases that there is no excess risk of cancer among adults living close to power lines, but the possibility of an association between some cancers and exposures to ELF magnetic fields is suggested by some occupational studies.

IARC classified ELF magnetic fields as possibly carcinogenic to humans (Group 2B) in its evaluation [14], while ELF electric fields were considered not to be classifiable as to their carcinogenicity to humans (Group 3). This evaluation only considers the likelihood of an association, but does not take into account the magnitude of the possible risk to individuals nor the population attributable risk. The results of epidemiological studies suggest that appreciable magnetic field effects, if any, are concentrated among relatively high and uncommon exposures.

Cellular telephones and cancer. The use of cellular phones and possible adverse health effects related to their use, attract much attention. Reports of brain tumour excesses occurring among phone users, case stories in the press and reports on thermal as well as magnetic effects on exposed tissue hypothesised to stimulate tumour growth, combined with the explosion in subscribers to cellular phones, raise public concern. The radiation from the cellular phones is characterised as non-ionising, alongside radar, microwave ovens and electrical wiring configuration. The radio frequency signals emitted from the devices range between 450 and 2200 MHz, i.e. in the microwave region of the electromagnetic spectrum.

A comprehensive review of the epidemiological literature was recently carried out by Boice and McLaughlin [15] and published by the Swedish Radiation Protection Authority. They conclude, after a review of nine major studies (two cohort studies on cancer, three hospital based case–control studies, one incidence population based case–control study and two prevalence based case–control studies), that no significant association is present for brain tumours and use of cellular phones, irrespective of duration of use, type of phone (digital or analogue), tumour morphology or laterality. The follow-up, however, is short, and even if relative risks are unlikely to exceed 1.3 it is important to monitor this exposure to exclude the possibility of any long-term effects. On the other hand, no biological mechanism supports a causal relation and there is no evidence of adverse effects on laboratory animals.

There are public health programmes that could prevent cancers developing or increase the probability that a cancer may be cured

Early detection is an important factor in reducing the death rate from cancer, whether it is achieved by personal actions or through participation in organised public health programmes. Awareness of different visual body signs or symptoms that could easily be observed by anyone and that are possibly related to cancer is important. It is unequivocally established that cancer survival is better for early, localised disease than for the later stage, advanced forms of the disease. Thus, the earlier in the process that a cancer can be diagnosed and treated then the better this is for the patient. Potential symptoms of cancer should not be ignored, but should serve as a clear warning for the individual to consult his or her doctor for advice. The signs and symptoms described in Table 10 are not specific for cancer. When any one is present, the individual should see a doctor.

Much effort has gone into cancer screening and the development of methods for finding cancers at an earlier stage in their development and increasing the prospects of a cure. It is possible to make recommendations based on the available evidence.

Table 10. Cancer's early warning signs

See a doctor if you notice:
A lump
A sore which does not heal (including in the mouth)
A mole which changes in shape, size or colour
A new skin lesion which appears and continues to grow
Abnormal bleeding
See a doctor if you have persistent problems, such as:
A persistent cough
Persistent hoarseness
A change in bowel or urinary habits
An unexplained weight loss

8. Women from 25 years of age should participate in cervical screening. This should be within programmes with quality control procedures in compliance with *European Guidelines for Quality Assurance in Cervical Screening*.

In many developing countries, the uterine cervix is one of the most prevalent sites for cancer, comprising ~25% of all female cancers. In industrialised populations, the disease is less common. In eastern and central European populations, the annual age-adjusted (using the World Standard Population as reference) incidence rates for invasive disease are 15–25 per 100 000 women. In the Nordic countries, the annual incidence was 15–30 per 100 000 women before the start of large-scale mass screening programmes.

The effectiveness of screening for cervical cancer has never been demonstrated in a randomised trial. There is, however, sufficient non-experimental evidence showing the efficacy of screening using a cervical smear (Pap) test performed every 3–5 years. This is based on case–control and cohort studies and on time trends and geographical differences associated within screening. The largest of these is the collaborative study co-ordinated by the IARC which showed that eradication of the disease is an unrealistic goal and that maximal protection after a negative smear is about 90%, which remains roughly the same during several years after the test. This conclusion is in agreement with the results of studies on the natural history of the disease, which have shown that most preinvasive lesions progress to frankly invasive cancer only over several years.

The effects are somewhat smaller at a population level. In some of the Nordic countries, the reduction was about 80% in women in the age groups exposed most intensively to screening. In the mid-1980s, after several years of organised screening, the overall incidence was 5–15 per 100 000 woman-years.

Cervix cancer screening should be offered to all women over 25 years. There is limited evidence of benefit from screening in women aged over 60 years, though the likely yield of screening is low in women over age 60 since the incidence of high-grade cervical lesions declines after middle age. Screening this age group is associated with potential harms from false-positive results and subsequent invasive procedures. Stopping screening in older women is probably appropriate among women who have had three or more consecutive previous (recent) normal Pap smear results. Yield is also low after hysterectomy, which leaves some cervical tissue, and there is scant evidence to suggest that screening produces improved health outcomes.

An organised programme consists of several essential elements. Defining the population to be screened is important. Personal invitation is the single most important means of attaining high attendance, especially when it is combined with effective information through the mass media. Free service has also been shown to improve attendance. Quality assurance of all steps of the process, monitoring and constant evaluation of the proportion of cancer detected, false positives and false negative readings, are mandatory. Near maximal effectiveness is achieved by an organised programme with high coverage, in which screening is initiated at the age of 25 years and is repeated at three- or five-year intervals until the age of 60. Extension of this approach should be considered only if maximal coverage has been attained, the resources are available and the marginal cost-effectiveness of the recommended changes has been evaluated. *European Guidelines for Quality Control in Cervix Cancer Screening* have been developed and are widely followed in Europe.

Infection with certain strains of HPV, generally acquired sexually, is the most important risk factor for cervical cancer. With the use of (modern) HPV detection methods >90% of squamous cell cervical cancer and 75–85% of high-grade cervical intraepithelial neoplasia (CIN) lesions have detectable HPV DNA. Given the implication of HPV infection in cervical cancer, detecting HPV could represent an appealing screening method. A study of 2009 women having routine screening in England and Wales, showed that 44% of CIN lesions of grade 2/3 detected had negative cytology and were found only by HPV testing (for types 16, 18, 31 and 33): a further 22% were positive for HPV but demonstrated only borderline or mild cytological changes. However, 25% of CIN grade 2/3 lesions were not detected by the four HPV tests.

Routine HPV testing for cervical cancer screening is an important research topic at present as HPV infection is very common in women <30 years old, and what matters are those women over the age of 30 with a HPV infection that persists over a long period of time. HPV testing is still to be evaluated to find the role it could play in cervical cancer screening. It has the potential to become an important test in detecting cervix lesions in future and should be a current research priority.

9. Women from 50 years of age should participate in breast screening. This should be within programmes with quality control procedures in compliance with *European Union Guidelines for Quality Assurance in Mammography Screening*.

Mammography can detect breast tumours at a clinically undetectable stage. The results of the early randomised trials of mammographic screening demonstrated the value of this technique and led to the introduction of organised national programmes of

screening in several countries in 1986–1988. Reports from seven trials involving over half a million women subsequently indicated a reduction in mortality from breast cancer of ~25% in women invited to be screened. The reduction of mortality in those actually attending screening is about one third.

There is now considerable evidence that breast cancer screening with mammography is effective in reducing mortality from breast cancer. An overview of the Swedish trials reported relative risks of death of 0.71 in the group randomised to receive an offer of screening, with 95% CI 0.57–0.89 for women aged 50–59 years at entry. Results for women ages 60–69 were almost identical. When applied to a population, a well-organised programme with a good compliance should lead to a reduction in breast cancer mortality of at least 20% in women aged over 50.

The value of screening women aged <50 years is uncertain. No trials have had large enough statistical power to analyse these women separately. What recommendations should be made for mammographic screening of women aged between 40 and 49 is an important question that cannot currently be answered; over 40% of the years of life lost due to breast cancer diagnosed before the age of 80 years are attributable to cases presenting symptomatically at ages 35–49 years, frequently an age of considerable social responsibility.

Swedish workers have recently conducted an overview of four of their trials. The conclusions indicate that the benefit of breast screening, in terms of a reduction in breast cancer mortality of 21%, persisted for a median time of 15.8 years. In addition to this overview, two working groups have been convened. A working group of the IARC met in Lyon on 5–12 March 2002 and consisted of 24 experts from 11 countries. The quality of the seven trials was assessed and it was concluded that screening by mammography reduced mortality from breast cancer in women of 50–69 years of age. In women who participated in screening programmes this reduction was estimated at 35%. For women of 40–49 years, evidence for a reduction in mortality was too limited to reach a conclusion. The evidence is insufficient to recommend performing routine breast self-examination as a method of screening.

Forty years of clinical trials, the contribution of hundreds of scientists and health workers and the dedication of hundreds of thousands of women to participate in studies lasting for decades has resulted in adequate evidence to support the efficacy of mammographic screening for breast cancer, which now allows its transfer to the arena of public health care. Doctors and women should be assured that participation in organised screening programmes with high quality control standards is of benefit, provided appropriate investigation and treatment is available. *European Guidelines for Quality Control in Mammographic Screening* have been developed and are widely employed throughout Europe.

Special efforts should be made to encourage screening among the more deprived members of communities. It is important not to over-emphasise the benefit of screening, and to appreciate that mammographic screening is but one step in the total care of women with the disease. As had been shown by long-term established programmes in the UK, Sweden, Finland and The Netherlands recognition of the importance of the multidisciplinary team in the assessment of mammographic abnormalities spread into the symptomatic sector leading to the development of integrated multidisciplinary breast care centres. Staffed by dedicated surgeons, radiologists and pathologists working alongside breast care nurses, counselling and other support personnel, these centres offer the necessary care for women with breast cancer.

10. Men and women from 50 years of age should participate in colorectal screening. This should be within programmes with built-in quality assurance procedures.

The identification of a well-determined premalignant lesion, the adenomatous polyp, together with the good survival associated with early disease, make colorectal cancer an ideal candidate for screening. In the past quarter century, progress has been made in our ability to screen patients for colorectal cancer or its precursor state, using advances in imaging and diagnostic technology. Faecal occult blood guaiac test cards were first employed in the 1960s, the flexible sigmoidoscope was introduced in the mid-1970s to replace the rigid sigmoidoscope that had been first introduced in 1870, and colonoscopy has been available since 1970.

Four randomised trials have examined annual or biennial screening with faecal occult blood testing (FOBT), while there are only data available regarding sigmoidoscopy and colonoscopy from observational studies, with little yet from randomised trials. There is evidence from these randomised trials to support the use of FOBT, with a reduction in colorectal cancer mortality of ~16% (95% CI 9% to 22%) from a meta-analysis [27% reduction (95% CI 10% to 43%) among those screened]. The proposed screening interval is 2 years, though it has been judged that yearly examinations are cost-effective.

Flexible sigmoidoscopy is an alternative or complementary method of screening whose efficacy has been consistently demonstrated in observational studies. The higher sensitivity of colonoscopy over FOBT suggests that colonoscopy is more effective. A large randomised trial of sigmoidoscopy is underway which should have results in 2005 or 2006.

Despite the accumulating evidence showing that screening for colorectal cancer is worthwhile, most citizens of developed countries have not been screened for colorectal cancer by any means. While this situation persists the chance is being missed to prevent about one quarter of the 138 000 colorectal cancer deaths which occur each year in the European Union. Special efforts are required against colorectal cancer which is now the most common malignant disease in the population of the European Union.

11. Participate in vaccination programmes against hepatitis B virus infection.

About 18% of human cancers worldwide are currently attributable to persistent infections with viruses, bacteria or parasites. In the European Union this fraction is about 10%, and it is chiefly accounted by four cancer sites or types, namely cancer of the cervix uteri, liver, stomach and some haemo-lymphopoietic tumours. Knowledge about the role of infectious agents in the aeti-

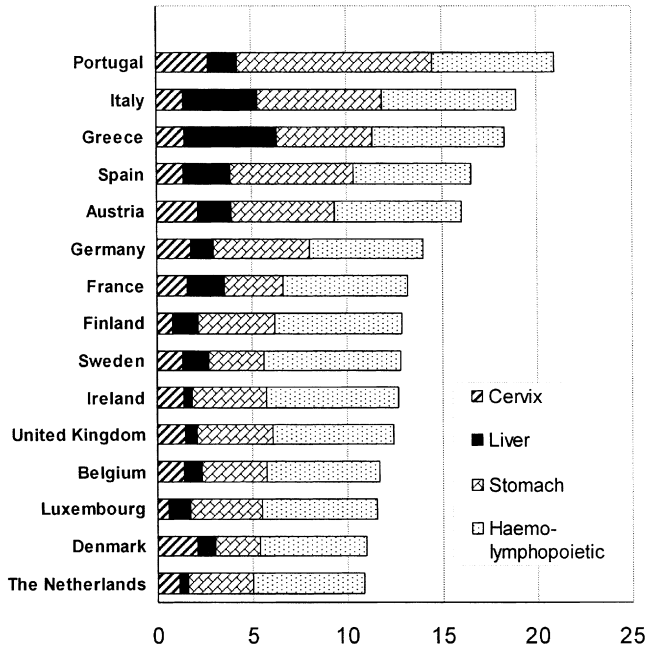

Figure 7. Cancer of the cervix, liver, stomach and haemo-lymphopoietic system as a percentage of all cancer diagnoses in both sexes in the European Union, 2000. Source Ferlay et al., 2000.

ology of several cancer types has rapidly expanded in the last 30 years, after major improvements were made in the detection of markers of chronic infection. Contrary to former beliefs, antibacterial and antiviral treatments, as well as vaccination programs, represent an important tool against cancer.

The four major cancer sites or types that have been linked to infectious agents (Figure 7) will be discussed below, with special reference to current opportunities for prevention in the European Union countries.

Every year ~25000 women in the European Union develop cervical cancer. A dozen types of HPV have been identified in 99% of biopsy specimens from cervical cancer worldwide, and in Europe HPV 16 has been reported in 56% of over 3000 cervical cancer specimens. Five HPV types (HPV 16, 18, 31, 33, 45) account for >85% of European cervical cancer specimens. In control women, the prevalence of the indicated HPV types is several dozen-fold lower. There is no effective medical treatment against HPV; however, very sensitive and specific tests for the detection of HPV DNA in cervical cells have become available. There is sufficient evidence for recommending HPV testing among women who show borderline or low-grade cytological abnormalities. Additionally, HPV testing improves the follow-up of women who have been treated for CIN lesions and, pending results of ongoing trials, may offer a more sensitive alternative to cytology in primary cervical cancer screening.

A prophylactic vaccine, based on late (L) 1 HPV 16 proteins, has been shown to be safe, highly immunogenic and efficacious in preventing persistent HPV infections in a trial of 1523 HPV 16-negative young women in the USA. A multivalent vaccine against the most common oncogenic HPV types may thus ultimately represent the most effective way to prevent cervical cancer worldwide, alone or in combination with screening. Vaccination would benefit women who do not attend screening programs in the European Union and, if combined with current screening programs, it would allow substantial savings (i.e. less frequent screening tests, fewer treatments, etc.).

Every year ~30000 new cases of liver cancer are recorded in the European Union. Upward trends in incidence and mortality rates have been seen in the last two decades, in men in France, Germany and Italy. Chronic infection with hepatitis B virus (HBV) and HCV accounts for the majority of liver cancer cases in Europe. In a large case-series of liver cancer from six European liver centres only 29% of 503 liver cancer patients had no marker of either HBV or HCV infection.

An effective vaccine against HBV has been available for 20 years now. Several countries in the European Union (e.g. Denmark, Finland, Ireland, The Netherlands, Sweden and the UK) do not perform routine vaccination against HBV in children, on account of the low prevalence of HBV infection in the general population (http://www.who.int/), whereas other countries (e.g. Belgium, France, Germany) report coverage below 50%. There is scope for reconsidering national policies regarding universal vaccination against HBV since selective vaccination of high-risk groups rarely works, and travelling and migration facilitate the mixing of high- and low-risk populations. Although infection with HBV in young adulthood (typically through sexual intercourse or contaminated needles) carries a much lower risk of chronic hepatitis and liver cancer than infection at birth or during childhood, it frequently induces acute hepatitis.

HCV represents an increasing problem in several areas of the European Union (especially Italy, Greece and Spain) and in some population groups, notably intravenous drug users. A vaccine is not yet available, and the effectiveness of treating all HCV RNA-positive individuals with pegylated interferon-2α with or without ribavirin is still under evaluation. Hence, the prevention of HCV infection relies for the moment on a strict control of blood and blood derivatives and avoidance of use of non-disposable needles in medical and non-medical procedures (e.g. acupuncture, tattooing, etc).

Helicobacter pylori (Hp) is associated with an ~6-fold increased risk of non-cardia gastric cancer. Out of ~78000 new cases of gastric cancer every year in the European Union some 65% may be attributable to Hp (assuming an Hp prevalence of ~35% in the general population). The current therapy of Hp infection, based on the use of proton-pump inhibitors and antibiotics, is efficacious but poor patient compliance, antibiotic resistance and recurrence of infection complicate the issue. Furthermore, although treatment of Hp infection can induce regression of gastric lymphoma, it has not yet been shown to reduce gastric cancer risk. Various approaches have been followed in the development of vaccines against Hp based on the use of selected Hp antigens, notably urease, the vacuolating cytotoxin (VacA), the cytotoxin-associated antigen (CagA) and the neutrophil-activating protein (NAP). Unfortunately, the natural history of Hp infection and the characteristics of an effective anti-Hp immune response are still poorly understood. Pharmaceutical companies seem to be reluctant to invest in the long and uncertain process of developing a vaccine

against Hp, an infection perceived as declining and amenable to medical treatment.

The fourth group of cancers where infectious agents are known or suspected to play a major role is haemo-lymphopoietic tumours [i.e. non-Hodgkin's lymphomas (NHL), HD and leukaemias]—a total of ~104 000 new cases per year in the European Union. Certain viruses [i.e. Epstein Barr virus (EBV), human immunodeficiency virus (HIV), human-T-cell leukaemia/lymphoma virus 1, Herpes simplex type 8 and HCV] and Hp account for an ill-defined proportion of NHL and HD. Childhood leukaemias may also be linked to one or more not yet identified infectious agents. As for Hp and gastric lymphomas, treatment of HCV has led to the regression of some extra-nodal NHL. Highly active antiretroviral therapy (HAART) has had a favourable impact on the occurrence of Kaposi's sarcoma, but not as yet of NHL, in HIV-infected patients. Recognising and treating infections linked to haemo-lymphopoietic tumours is a priority in the European Union, on account of the steady increase in the number of cases and high-risk individuals (e.g. iatrogenically immuno-suppressed and HIV-positive subjects).

In conclusion, infectious agents account for a substantial fraction of cancers in the European Union. For the moment, priorities are the expansion of immunisation programs against HBV and the inclusion of HPV testing in cervical cancer screening programs. Vaccines against cancer-causing infectious agents are, however, one of the most promising ways to prevent or even cure some important tumours. Because of the enormous cost of vaccine development, public–private partnerships [e.g. the Global Alliance for Vaccines and Immunisation (GAVI) for developing countries] should be actively pursued in the European Union, especially with respect to the development of vaccines against HCV and Hp.

Additional items considered

The committees discussed a number of other issues in cancer epidemiology and cancer control and decided that the situation was not so certain that any recommendation could be made with a convincing probability of success in reducing cancer risk. Issues considered included chemoprevention, exogenous hormones and screening for other forms of cancer.

Chemoprevention

β-*carotene.* While observational epidemiological studies have consistently shown that β-carotene is associated with decreased cancer risk, particularly of lung cancer, findings of seven randomised trials testing the effect of β-carotene supplementation on cancer incidence and mortality generally have not been supportive. Two of these trials even suggested the possibility of harmful effects.

Two large trials of β-carotene conducted among persons at average risk of cancer found no statistically significant benefit or harm associated with β-carotene supplementation [16, 17]. Two other large trials tested β-carotene among persons at high risk of cancer [18, 19]. One reported a statistically significant (18%) increase in lung cancer incidence after 5–8 years of treatment with β-carotene among male Finnish smokers [18]. Another, which used a combination of β-carotene and retinol, reported a statistically significant (28%) increase in lung cancer incidence among American smokers, former smokers and asbestos workers [19].

Only one large trial, which tested a combination of β-carotene, vitamin E and selenium in a poorly nourished Chinese population, found that after 5 years, the treated group experienced a statistically significant (9%) reduction in total mortality, primarily as a result of a statistically significant (21%) lower stomach cancer mortality rate [20]. The (indirect) evidence that β-carotene may protect from stomach cancer comes from the randomised, controlled double-blinded chemoprevention trial in subjects with gastric dysplasia in an area with a very high gastric cancer risk in Columbia. Gastric biopsy taken at baseline was compared with those taken at 72 months. Treatment with 30 mg β-carotene resulted in a statistically significant increase in the frequency of regression of preneoplastic lesions of the stomach [relative risk (RR) = 5.1, 95% CI 1.6–14.2] [21]. One small trial of 1805 people with previous non-melanoma skin cancer that tested treatment with β-carotene (50 mg/day) to reduce the occurrence of new skin cancer did not find any effect of this intervention [22].

It can be concluded that there is evidence at present that β-carotene supplements have no value as cancer chemoprevention agents and cannot be recommended for use in the general population in this context.

Vitamins A, C and E. In all trials in which the preventive effects of these vitamins have been studied, they were used in different combinations and therefore it is impossible to assess the effect of each of these micronutrients separately.

No significant effects on mortality rates were observed for supplementation with combinations of retinol and zinc [20] or β-carotene and vitamin A [19]. Supplementation with ascorbic acid (1 g twice per day) was associated with increases in the rates of regression of dysplastic lesions in the stomach [odds ratio (OR) = 5.0; 95% CI 1.7–14.4] [21], whereas in a trial in Linxian (China) supplementation with vitamin C and molybdenum had no effect on overall and cancer mortality [20].

In the study in Linxian, the intervention group receiving supplementation with vitamin E, β-carotene and selenium experienced a statistically significant (9%) reduction in overall mortality and 13% reduction in cancer mortality, which was mainly due to lower stomach cancer rates (OR = 0.79; 95% CI 0.64–0.99) [20]. In the α-Tocopherol, β-Carotene Cancer Prevention Study Group [18] trial α-tocopherol had no apparent effect on total and cancer mortality.

It can be concluded that there is no evidence at present that vitamin A, ascorbic acid or α-tocopherol supplements have value as cancer chemoprevention agents and they cannot be recommended for use in the general population in this context.

Selenium. In three large randomised placebo-controlled trials, selenium supplementation was given either alone [23] or with other elements [20, 24].

Clark et al. [23] carried out a study in the USA on 1312 subjects to test whether selenium supplementation could reduce the incidence of non-melanoma skin cancer. Although no benefit was

found for skin cancer, the group receiving the supplement had statistically significant reductions of ~40% and 50% in overall cancer incidence and cancer mortality, respectively. Based on these findings, there is a large randomised trial of selenium and prostate cancer prevention on-going.

The other two studies were conducted in Linxian, China. In the smaller study multivitamin supplements containing selenium was randomly assigned to 3318 people with pre-existing oesophageal dysphasia. At the end of a 6-year intervention period the group receiving the supplement had statistically non-significant reduction of 7% in total mortality and 8% oesophageal/gastric cardia cancer mortality [24]. In the larger Linxian trial, 29584 participants were assigned to receive four combinations of different nutrient supplements for 5 years. The group receiving the supplement with selenium, β-carotene and vitamin A had a statistically significant reduction of 9% in all cause mortality and 13% in cancer mortality. In these two Chinese studies it is impossible to disentangle the effect of selenium from effects of other micro-elements [20].

It can be concluded that at present there is at most weak evidence that selenium supplements have value as cancer chemoprevention agents and they cannot be recommended for use in the general population in this context.

Fibre. In five randomised trials, dietary supplementation with wheat bran or other types of fibre did not affect the rate of recurrence of colorectal adenomas. Two studies tested the effect of dietary counselling to reduce fat consumption and increase fibre intake [25, 26]. In one study the subjects in the intervention group were advised to increase fat intake and take wheat-bran supplement [27] and two studies tested purely the effect of fibre supplements [28, 29].

The results of the Toronto Polyp Prevention Trial [25] (randomised, not blinded) suggest that there was no significant difference in polyp recurrence between persons assigned to low fat/high fibre diet and those following a normal western diet. The ratio of cumulative incidence rates was 1.2 (95% CI 0.6–2.2) [25]. In a randomised (not blinded) control trial in which the intervention group was assigned to the low fat, high-fibre (18 g per 1000 kcal) and high fruit and vegetable diet, no difference was observed in recurrence rate of colorectal adenomas (and large adenomas) between intervention and control group, who followed their usual diet. The unadjusted risk ratio was 1.00 (95% CI 0.90–1.12) [26].

In the Australian randomised (not blinded) trial of intake of fat, fibre and β-carotene to prevent colorectal adenomas there was no significant prevention of new adenomas in any of treatment groups [27]. In a double-blind randomised study, a dietary supplement of wheat-bran fibre had no statistically significant effect against recurrent colorectal adenoma. The multivariate adjusted OR for recurrent adenomas in the high-fibre (13.5 g per day) group compared with the low-fibre (2 g per day) group was 0.88 (95% CI 0.70–1.11; $P = 0.28$); and the OR of recurrence according to the number of adenomas in high-fibre group compared with the low-fibre group was 0.99 (95% CI 0.71–1.36; $P = 0.93$) [28].

In a randomised controlled study that tested the protective effects of supplementation with fibre (3.5 g ispaghula husk) and calcium (2 g daily) on colorectal adenomatous polyp recurrence, the adjusted OR for recurrence in the fibre treatment group was 1.67 (95% CI 1.01–2.76; $P = 0.42$). The OR associated with the fibre treatment was significantly higher in participants with baseline dietary intake above the median than in those with intake below the median (interaction test, $P = 0.028$) [29].

It appears from the results of these randomised trials that supplementation with fibre does not affect the risk of the recurrence of colorectal polyps. The evidence of a protective effect of fibre against colorectal cancer is purely observational and the use of fibre cannot be recommended for the general population at the present time.

Calcium. In a randomised double-blind study involving 913 patients, Baron et al. [30] observed that calcium supplementation (1200 mg of elemental calcium daily) moderately reduced the risk of recurrence of adenomatous polyps of the large bowel. The adjusted risk ratio for any recurrence of adenoma with calcium compared with placebo was 0.85 (95% CI 0.74–0.98, $P = 0.03$). The adjusted ratio of the average number of adenomas in the calcium group to that in the placebo group was 0.75 (95% CI 0.60–0.96, $P = 0.02$). The effect of calcium was independent of initial dietary fat and calcium intake [30].

The randomised double-blind 3-year intervention study by Hofstadt et al. [31] showed that a mixture of calcium and antioxidants had a beneficial effect on adenoma recurrence, though not on adenoma growth; the effects of calcium could be disentangled from those of antioxidants. In the study of Bonithon-Kopp et al. [29], which tested the efficacy of fibre and calcium supplements in prevention of colorectal neoplastic polyp recurrence, the rate of recurrence was statistically non-significantly decreased in the calcium (2 g daily) treatment group. The adjusted OR for recurrence was 0.66 (95% CI 0.38–1.17; $P = 0.16$)

The evidence suggesting that calcium supplementation decreases risk of colorectal adenomas is not yet sufficient to recommend its use to the general population as a strategy to prevent colorectal cancer.

Nonsteroidal anti-inflammatory drugs (NSAID). Numerous observational epidemiological studies have found that long-term users of aspirin or other NSAIDs have a lower risk of colorectal adenomatous polyps and colorectal cancer than non-users. Randomised clinical trials have confirmed that two NSAIDs, the prodrug sulindac and selective cyclooxygenese (COX)-2 inhibitor celecoxib, effectively inhibit the growth of adenomatous polyps and cause regression of existing polyps in patients with familial adenomatous polyposis (FAP) [32, 33]. Less promising are results on the far more common sporadic adenomatous polyps. Treatment with sulindac did not result in regression of sporadic adenomas [34] or doses required to achieve the effect may cause toxicity, which outweighs the benefits of treatment [35].

Despite some positive results obtained in studies in humans and coupled with biological plausibility [36], the efficacy of long-term NSAIDs prophylaxis against colorectal cancer, and other cancers,

remains unproven. Recommendations regarding the use of NSAIDs for prevention of colorectal cancer, except probably the use of celecoxib or sulindac for control of the growth of colorectal adenomas among patients with FAP, appears to be premature at the present time.

Tamoxifen. Five trials have now reported on the use of tamoxifen and raloxifen for prevention of breast cancer [37–41]. Four trials compared 20 mg tamoxifen daily for at least 5 years with placebo [42]. One trial compared two doses of raloxifen (60 mg or 120 mg) with placebo [41]. Cuzick et al. [42] report an overview of the main outcomes of these prevention trials and adjuvant trials in which tamoxifen treatment was given for at least 3 years with doses of 20–40 mg. The combined data from tamoxifen prevention trials supported a reduction in breast cancer incidence by 38% (95% CI 28% to 46%; P <0.001). The adjuvant studies and the raloxifen trial showed greater reductions (46% [95% CI 29% to 63%] and 64% [95% CI 44% to 78%], respectively). There was no effect for breast cancers negative for oestrogen receptors (ER), but ER-positive cancers were decreased by 48% (95% CI 36% to 58%). Rates of endometrial cancer were increased in tamoxifen prevention trials (RR = 2.4, 95% CI 1.5–2.6). No increase has been seen with raloxifen. Venous thromboembolic events were increased in all tamoxifen studies and with raloxifen.

The evidence now clearly shows that tamoxifen can reduce the risk of ER-positive breast cancer. However, high rates of side-effects do not permit a recommendation of the prophylactic use of tamoxifen in healthy women based on current evidence.

Exogenous hormones

Oral contraceptives. Over the last decade, several epidemiological studies have been published on the oral contraceptives (OC) and cancer risk issue. These studies were reviewed in June 1998 by an IARC Working Group, and are summarised in the IARC monograph 72 [43].

A collaborative reanalysis of individual data on 53 297 breast cancer cases and 100 239 controls indicated that there is a moderate excess risk for this disease among current or recent OC users, which tends to level off in the few years after stopping use. OC use has also been found to be positively associated with cervical cancer risk in HPV-positive women. Conversely, OC (with the exception of the currently not used sequential type) reduce the risk of endometrial cancer. Further, data on ovarian cancer indicate a long lasting protection from OC use, which may well be evident up to 20 years after cessation. Several studies have suggested an inverse relation between use of OC and risk of colorectal cancer, but no association with duration of use was observed. An increased risk for OC users of hepatocellular carcinoma is considered as established.

The main established evidence on the OC and cancer issue can be summarised as follows:

- There is a small increased risk of breast cancer among current users, but not among former users who have ceased for 10 or more years.
- OC lower the risk of endometrial and ovarian cancer, and the protection seems to persist after cessation of use.
- A reduced risk of colorectal cancer among OC users is possible, but this issue is still open to discussion.
- OC are related to increased risk of cervical cancer and liver cancer, but the public health importance of these associations is small in developed countries.
- OC have been used for 40 years, and the formulations have been modified repeatedly. It is therefore difficult to propose further modifications that may appear favourable on the risk of selected diseases without increasing the risk of other side-effects.

Hormonal replacement therapy. Hormonal replacement therapy (HRT) has been reported to increase breast cancer risk. In a collaborative reanalysis of individual data from 51 epidemiological studies including >52 000 women with breast cancer and 108 000 without breast cancer, breast cancer risk increased by ~2.3% per year of use, but dropped after cessation of use. There is evidence that combined oestrogen–progestogen HRT may be associated with higher risk of breast cancer compared with unopposed oestrogens. In contrast, unopposed oestrogen use, but not combined oestrogen–progestogen treatment, has been strongly related to endometrial cancer risk in observational studies.

HRT has also been reported to be positively associated with ovarian cancer risk, and inversely to colorectal cancer risk.

Important information on cancer risk in users of combined estrogen and progestogen HRT comes from the Women's Health Initiative (WHI), a randomised primary prevention trial including 8506 women aged 50–70 years treated with combined HRT and 8102 untreated women. The combined treatment group was closed in May 2002, whereas an additional oestrogen only group is still ongoing (as of November 2002). With respect to breast cancer, no difference in risk was evident for the first 4 years after starting treatment, but an excess risk was evident thereafter. At the 7 years follow-up, 166 breast cancer cases were registered in the treated group versus 124 in the placebo group, corresponding to a RR of 1.24 (95% CI 1.03–1.66). Data from two other smaller randomised studies are available, one Heart and Estrogen/progestin Replacement Study (HERS) with combined oestrogen–progestogen therapy, and one (WEST) with estrogen only. In a combined analysis of the three randomised trials, 205 cases of breast cancer were registered in the treated groups versus 154 in the placebo, corresponding to an overall RR of 1.27. Since, however, this estimate is heavily weighted by the WHI study, the quantitative role of estrogen only HRT on breast cancer risk cannot be conclusively documented.

Data on endometrial cancer are available from the WHI and the HERS study, both based on combined therapy. Overall, 24 cases were observed in the combined HRT groups versus 30 in the placebo groups, corresponding to a pooled RR of 0.76.

With reference to colorectal cancer, the combined analysis of the WHI and HERS studies included 56 cases in the HRT treated group and 83 cases in the placebo group (RR = 0.64).

Thus, with reference to HRT and cancer risk, the recent findings of randomised trials are in broad agreement with those of observational (cohort and case–control) studies, and therefore provide strong evidence that:

Table 11. Cancers and screening methods that have been shown to be worthwhile, those that are of unknown value and those that are known to be not worthwhile

Cancer site	Method
Screening worthwhile	
Breast	Mammography
Cervix	Cervical cytology
Colon/rectum	Faecal occult blood
Value of screening unknown (research in progress)	
Prostate	Prostate specific antigen
Stomach	*H. Pylori* testing; radiographic/endoscopic stomach examination
Colon/rectum	Flexible sigmoidoscopy
Ovary	CA125 and/or ultrasound
Breast	Mammography in women <50; BRCA1 and 2 mutation in Jewish women
Cervix	Human papilloma virus testing
Lung	Spiral computed tomography (CT)
Skin cancer (Melanoma)	Examination for moles
Oral cancer	Examination of the mouth
Screening not worthwhile	
Neuroblastoma	Urinary homovanillic acid (HVA) and vanillylmandelic acid (VMA)
Lung cancer	Chest X-ray
Breast	Breast self-examination
Testis	Self-examination (because modern treatment after clinical presentation is so effective)

- Combined oestrogen–progestogen HRT is associated with a moderate excess risk of breast cancer, which becomes evident after a few years of use. Such an increased risk appears to be restricted to current users.
- The pattern of risk in relation to HRT use appears similar for ovarian cancer, although data remain inadequate.
- Unopposed estrogens are strongly related, but combined HRT is not associated to, a material excess risk of endometrial cancer.
- HRT may have a favourable effect on colorectal cancer risk, although the relation with duration and other time-related factors remains unclear.
- Considering also the apparently adverse effects of HRT on cardiovascular diseases, HRT should not be recommended for disease prevention. HRT remains indicated for short-term symptom relief, while other treatments should be considered for osteoporosis.

Screening for other forms of cancer

Screening has been defined as the systematic application of a test or inquiry to identify individuals at sufficient risk of a specific disorder to benefit from further investigation or direct preventive action, among persons who have not sought medical attention on account of symptoms of that disorder. Before a screening test can be introduced it is necessary to be able to demonstrate that the test not only distinguishes people who will develop the disease from those who will not, but that a remedy is available to individuals who are judged to be screen-positive that can significantly improve their health compared with not screening, and treating the disease on clinical presentation in the usual way.

In assessing screening tests for cancer, a large randomised trial is usually necessary. This would compare mortality from the specific cancer in a group that has been screened and treated with the corresponding mortality in an unscreened group that received treatment only after clinical presentation. In screening programmes that aim to detect cancer lesions at an early stage it is impossible to determine the proportion of all of the cancers in question that would have presented clinically over a specified period that are detected by screening, because cancers cannot be detected without then intervening. The outcome of screening trials is therefore expressed as a proportional reduction in mortality from the specific cancer and then a judgment made as to whether this is worthwhile.

Table 11 shows the cancers and screening methods that have been shown to be worthwhile, those that are of unknown value and those that are known to not be worthwhile. Breast cancer screening by mammography in women aged over 50 years can reduce mortality from the disease by ~30%. Screening for colorectal cancer by FOBT can reduce mortality from the disease by ~15%. Both rates were shown using randomised trials. Screening for cancer of the cervix by cervical cytology has been judged to be worthwhile (~80% reduction in mortality from this disease), though without evidence from randomised trials.

A difficulty with screening is that some cancer screening programmes have been introduced in the absence of evidence that they are worthwhile, for example, prostate cancer screening, and breast cancer screening in women aged under 50 years. It is

important that health authorities resist the temptation to introduce population screening programmes until there is firm evidence of efficacy, as judged by a reduction in mortality from the cancer in question. The presumption of benefit should not be sufficient grounds for introducing large scale programmes.

Sometimes an effective screening test [e.g. prostate-specific antigen (PSA) for prostate cancer] has led to the introduction of screening programmes in the absence of trial results showing evidence of benefit in terms of disease prevention. Once such services are in place they can be difficult to stop. Then existing data should be used to try to evaluate efficacy, albeit in a less than ideal manner.

There is a general need to continually evaluate screening services to ensure that the performance expected from the results of randomised trials and other relevant research can be achieved in practice. Service provision will depend on available resources and the burden of disease from the cancer in question in the absence of screening.

The following cancer screening programmes should be made generally available:

1 Screening for breast cancer by 3 yearly mammography examinations for women from the age of 50 years.
2 Colorectal cancer screening by FOBT every 2 years from the age of 50 years.
3 Cervical cancer screening by 5 yearly cervical smear examinations for women from the age of 25 years.

Others should not be offered as services at all or should be part of research programmes designed to determine their value. There are screening tests available and being evaluated for stomach cancer, oral cancer, nasopharynx cancer and neuroblastoma. Screening for prostate cancer and screening for lung cancer are, however, the subject of much recent research.

Screening for prostate cancer. At the present time there is pressure to screen for prostate cancer, but implementation of screening programmes for prostate cancer cannot be recommended based on the available evidence. The main reason for this situation is that no results are available from randomised trials assessing screening for prostate cancer. These are the only methods of evaluation which avoid bias and, in consequence, it is not known whether screening by one of the available modalities or in combination is effective in leading to a reduction in the mortality rate from prostate cancer. This is a necessary prerequisite for embarking on population screening.

Any reduction in mortality from prostate cancer due to screening, while uncertain, must be weighed against the harm from screening diagnosis and treatment. Some men who do not need treatment are likely to receive it. These are men destined to die of causes other than prostate cancer. Unfortunately, at diagnosis, men needing treatment for prostate cancer cannot be differentiated from men who do not.

The PSA test is simple, cheap, readily available and acceptable. PSA testing has already achieved a high penetration among men and their physicians. To document the extent of PSA testing in the general population at Getafe (Spain) a total of 5371 PSA test records (1997–1999) were reviewed and testing rates estimated per 1000 person-years. The PSA-testing rate in the general population was 21.6/1000 person-years. In the age-group 55–69 years, this rate was 86.8/1000 and increased to 152.6/1000 in men >70 years. In Milan, Italy where there is no campaign publicising or encouraging prostate cancer screening, it has been estimated that 26.9% of men aged 40 and older and without a history of prostate cancer received a PSA test in the 2-year period 1999–2000. In men aged 50 and greater, this rate rose to 34%.

Multiple sources of data show that prostate cancer incidence rates rose following the introduction of PSA testing. The average age at diagnosis has fallen, the proportion of advanced stage tumours has declined, the proportion of moderately differentiated tumours has increased, and patterns of care have changed accordingly. A decline in mortality began in the USA and other countries in 1991. The decline in mortality is well established, but this recent trend may only retrace an increase in mortality that immediately preceded it. The descriptive epidemiology of prostate cancer reveals many effects of the introduction of prostate cancer screening. Although the evidence suggests increased prostate cancer testing has yielded public health benefit, this has not yet been shown conclusively and a decision on the value of screening should await the results of trials. In any event, systems should now be in place to ensure that men and physicians participating in PSA testing participate in a programme in which the effect of the intervention can be evaluated as best can be done given the non-experimental nature of the intervention.

Screening for lung cancer. It has long been established that the best way to control lung cancer is to reduce cigarette smoking in the population, foremost through prevention, and secondarily through smoking cessation. However, even after stopping smoking long-term smokers remain at high risk of lung cancer. Lung cancer when clinically diagnosed has a poor outcome with 10–16% survival at 5 years. If the tumour is small enough to be removed surgically, the outcome is much better, >70% for stage I tumours. This led to speculation in the past as to whether long-term smokers or others at high risk might benefit from earlier detection.

Low-dose spiral CT scanning can detect lung cancer at an early stage. The Early Lung Cancer Action Project (ELCAP) demonstrated that spiral CT was able to identify very small lung cancers in high-risk volunteers, with a resectability rate of 96% and a proportion of stage I >80%. An initial high false-positive rate was reduced by high-resolution CT (HRCT) with a complex algorithm of 3D reconstruction for tumour growth. Randomised trials of spiral CT using a non-intervention control group and with lung cancer mortality as the trial outcome are needed to determine the value of this method of screening.

Genetics

A clearer understanding of carcinogenesis is emerging with our rapidly expanding knowledge of genetics. At the same time there remain issues surrounding genetics and genetic testing, which are very important. Cancer results from a breakdown in the genetic control of cell growth and behaviour. The study of genetic changes associated with different types of cancer has been under-

way for over 40 years and has become central to the diagnosis and management of many cancers. For example, most leukaemias are associated with specific chromosomal rearrangements that activate the genetic messages which stimulate growth of that cell type. One of the earliest discoveries, the Philadelphia chromosome in chronic myeloid leukaemia, was later shown to involve a translocation joining together pieces of chromosomes 9 and 22. This produced an abnormal gene capable of generating a tyrosine kinase like product. Recently, a highly effective drug designed to block that gene product, imatinib, has been approved for clinical use.

It is now essential for the effective management of most leukaemias to have access to high quality cytogenetic diagnosis. These techniques are being extended into the use of molecular diagnostic techniques. A good example is detection of the characteristic amplification of the proto-oncogene *Nmyc* in neuroblastoma and *her2* in breast cancer. These changes are somatic errors, mistakes which arise in a cell in the body at some time after conception. In almost all cases, a series of genetic errors must occur before a cell becomes capable of uncontrolled growth and spread to other sites. In some individuals, a genetic error in the germline that predisposes them to cancer affects every cell in the body. Such changes can be inherited, resulting in families with multiple affected members. The last decade has seen an upsurge in discoveries of the genes that underlie these hereditary forms of cancer. The attraction of this research has been that it provides a means of more accurate diagnosis, and in some cases allows presymptomatic diagnosis. Any gene which, when defective, predisposes to malignancy is usually a key part of an important pathway. As a result, discovery of these genes has led to a better understanding of the causes of common cancers.

The classic example is the *APC* gene on chromosome 5 which underlies the rare dominant syndrome FAP. In most colorectal adenocarcinomas both copies of this gene are inactive, a change which is apparent in early adenomas. The identification of a pathological mutation in the *APC* gene, typically a frameshift mutation distal to the catenin binding site in exon 15, is of great clinical value as it allows accurate identification of other family members who will need regular endoscopy and prophylactic surgery. Of equal importance is the ability to discharge with confidence those family members who have not inherited the defective copy of the gene. A range of similar cancer syndromes are now amenable to molecular diagnosis; multiple endocrine neoplasia, Von Hippel Lindau syndrome, juvenile polyposis and neurofibromatosis type 2 are important examples of dominant syndromes. Recessive syndromes include Fanconi's anaemia and Bloom's syndrome, both of which are examples of defective DNA repair. Provision of diagnostic services for such disorders needs to be organised at regional, national and sometimes supranational levels to ensure an appropriate level of quality assurance and technical expertise.

A second and more problematic category of molecular diagnosis has become possible in the last decade; several genes have been identified which, when defective in the germline, predispose to a high penetrance form of one of the common forms of cancer. Such patients lack the characteristic syndromic features that allow easy targeting of molecular genetic expertise. The breast/ovarian cancer predisposition genes *BRCA1* and *BRCA2* and members of the mismatch repair gene family, such as *MSH2* and *MLH1* that predispose to colorectal cancer and endometrial cancer among others, are the classic examples of this category. These are large genes in which many hundreds of pathological changes are possible. Distinguishing causative mutations from harmless population variants in families with multiple affected members is a major challenge, which is being met through international cooperation. Methods of rapid analysis of such genes are becoming available. In the foreseeable future it is likely that all breast, ovarian, colorectal and endometrial cancers will be checked for germline mutations in these and similar genes so as to better characterise the cancer and allow more effective therapy. In the meantime, limited diagnostic resources must be targeted at those individuals most likely to generate a result of diagnostic value.

Mutation detection in the mismatch repair genes is best focused on affected individuals who are part of a family that satisfies the modified Amsterdam criteria. These were designed to identify useful research families, but are also valuable in targeting diagnostic resources. Suitable individuals belong to families in which there have been at least three cancers in people where one is a first degree relative of the other two. For example, a woman, her son and her brother. Provided they have colorectal cancer and/or endometrial or gastric cancer and one had onset before 50 years of age, there is a >90% probability that a mutation in *MSH2* or *MLH1* will be detected. Almost all tumours resulting from defects in these mismatch repair genes display a characteristic instability of the DNA microsatellite markers used in traditional genetic linkage studies. Immunohistochemistry for the protein product of *MSH2* is also valuable as its absence is a strong indication of mutation in the *MSH2* gene. This technique is less effective for *MLH1* because a large proportion of sporadic colorectal cancers lose expression of this protein due to a reversible suppression of gene expression.

Mutation detection in the *BRCA* genes is best focused on families where there have been at least four affected individuals in multiple generations. Families that feature breast and ovarian cancers, bilateral cancers in young women and male breast cancer are all worthy of diagnostic testing. The primary problem is the slow development of these molecular diagnostic services. Urgent investment in laboratory facilities and staff training is needed to prepare for the expansion of diagnostic need. It is estimated that overall at least 5% of the common cancers other than lung cancer have a single gene defect underlying them that would be amenable to predictive testing and more effective prevention and therapy. In pure health economic terms the benefits are obvious of catching early a solid tumour allowing cure rather than prolonged palliation of cases diagnosed later. Unfortunately, the financial benefits of cure affect different aspects of health care to the services called upon to deliver diagnostic genetic services. There is a willingness of European genetics centres to integrate their work. This is threatened by the need to compete in a more commercial setting and by the patenting of genes such as *BRCA1*. Gene patenting can hamper the rapid development and dispersal of diagnostic tests and is likely to restrict fulfilment of the potential of genetic testing in cancer prevention.

The next phase of genetic discovery will be to identify genes that contribute to the heritable component of the cause of cancer, but are not sufficiently influential to account for families with a classic pattern of inheritance of cancer. The gene *CHEK2* occupies a critical role in cell cycle control. Association studies within cases of familial breast cancer have identified mutations in this gene as being a significant risk factor in predisposition to breast cancer. In most cases, defective function of at least one other unidentified gene is needed to precipitate disease. Such genes, which confer a mild to moderate increase in predisposition, are likely to interact with environmental triggers to lead to cancer in a proportion of people with the at risk genotype. These developments will lead to a growing list of genetic variations in the population being identified as conveying an increased risk of malignancy. The major challenge will be to quantify the risk associated with such genetic variation in different environmental settings. It is likely that a range of biases will lead to several such associations being assigned an inappropriate significance. Large scale population based evaluation will be needed, such as will become possible with the new Biobank UK project, before these moderate risk genes can be incorporated into clinical practice.

Cancer mortality trends

The total number of cancer deaths will be influenced by both the size and the age distribution of the population. Age standardised mortality rates have to be used to adjust for these. To measure the effect of the third version of the *European Code Against Cancer* on cancer mortality, reliable estimates are needed for the near future, taking the recent trends in mortality and the projected populations into account. Age standardised cancer mortality rates and numbers of cancer deaths have been estimated for the period 2000–2015 using the most recent cancer mortality data and statistical models.

Mortality data were obtained from the WHO database: long time series were available for all 15 European Union countries and for five of the 10 applicant states including the Czech and Slovak Republics for which data were combined to give the necessary time span of data for input into the statistical models (see below). Only recent data were available, however, for Estonia, Latvia, Lithuania and Slovenia. [More historical data for the three Baltic states and Slovenia will become available shortly.] No data were available for Cyprus. Population estimates in 5-year age groups from the 1950s to 2000 for each country were also obtained from the WHO database. Corresponding population projections up to 2020 were obtained from the United Nations database.

Mortality rates were modelled as a function of age, calendar period and birth cohort. Birth cohort was calculated as age subtracted from calendar period. Since the data were aggregated into 5-year age groups and 5-year calendar periods, the birth cohorts are synthetic and partly overlapping

The general result from the forecasting of the future age specific cancer mortality rates was that, in most countries, the age standardised rates are predicted to decrease; both the timing and the extent of the decreases vary considerably among the countries. Results for the individual cancer sites indicated that the overall trends were largely dependent on the decreasing rates in lung cancer mortality in males, and in breast cancer mortality in females.

As a consequence of the generally decreasing trends in the age standardised rates, the best estimate is that there will be ~1.25 million cancer deaths in 2015, which is over 130 000 (11%) more deaths than in 2000, but 155 000 (11%) fewer deaths than projected in 2015 on the basis of demographic changes alone. The increases in the forecast numbers of cancer deaths in 2015 are proportionally larger in males than in females (13% and 10%, respectively) and proportionally larger in the applicant states than in the current European Union member countries (14% and 11%, respectively).

Future directions

A key element of the future will be the rapid emergence of new technologies, some of which may have important impacts on several aspects of cancer prevention, diagnosis and treatment. Remarkable strides have been made in a number of technology fields but their application to cancer medicine will take another decade or so. It was thought to be of interest, nevertheless, to indicate how new methodologies might begin to influence the areas of cancer detailed in this code.

The most readily applicable new technologies are in imaging, molecular typing of tissues and intelligent drug design.

It is possible that spiral CT examination of the lungs of smokers might be shown to dramatically improve early detection of resectable lung tumours. On the other hand it is quite unlikely that sophisticated second generation nuclear magnetic resonance imaging or positron emission tomography scanning will be routinely applied to populations, even those at high risk. Rather they could be useful in characterising suspicious lesions and of course in delineating primary tumours and suspect metastases. Virtual colonoscopy, on the other hand, may prove to be a valuable way to screen for bowel cancer, as may stool examination, not for blood, but for the presence of mutated genes in sloughed cells.

Unravelling the molecular constitution of tissues is already a reality, though not in any routine application. Thus tumour cells in small numbers can be arrayed by gene and protein chip technology to reveal a molecular signature, specific to that tumour. Perturbed patterns of gene and protein expression have already been used to reclassify tumours, and to correlate with eventual prognosis. Certain drug treatments and radiation regimes have been correctly predicted to be ineffective in the environment of specific genetic mutations. And, of course, a couple of specific examples exist where targeted therapeutics, antibodies (such as trastuzumab against her2-neu moieties) and small molecules (such as imatinib against bcr-abl kinases), have become effective treatments. In these and some other instances, gene and protein technology has been used to monitor treatment, providing extremely precise molecular end points.

Molecular examination of normal cells in a cancer patient may also give a guide to the metabolic fate of a range of medicines. Using this information, a number of drugs may be discarded as

inappropriate for that person. The era of truly tailor-made treatment may not be far off.

The new technologies mentioned above may provide opportunities for development of new diagnostics, e.g. for virus-associated malignancies; they may be helpful in the analysis of large population-based sets of tissues and offer new insights into mechanisms of interaction between environmental factors, e.g. dietary components and genotype; and they may be helpful in selection of high risk volunteers for specific tailored chemoprevention trials. All told, the future appears to be full of bright promise in cancer control and the challenge is to fulfill that potential.

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Suggested reading

There are key references proposed for more detailed information and background regarding the points presented above in outlining the rationale behind the recommendations made for the revised *European Code Against Cancer*. These are presented below separately for each of the points described above.

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